



US009206179B2

(12) **United States Patent**  
**Liu et al.**(10) **Patent No.:** **US 9,206,179 B2**  
(45) **Date of Patent:** **\*Dec. 8, 2015**(54) **METHODS OF USE COMPRISING  
DEUTERATED  
PYRAZINO[2,1-A]ISOQUINOLINES**2007/0197695 A1 8/2007 Potyen et al.  
2008/0103122 A1 5/2008 Veltri  
2012/0149709 A1 6/2012 Liu et al.(71) Applicant: **Concert Pharmaceuticals, Inc.,**  
Lexington, MA (US)(72) Inventors: **Julie F. Liu**, Lexington, MA (US); **Scott  
L. Harbeson**, Cambridge, MA (US);  
**Roger D. Tung**, Lexington, MA (US)(73) Assignee: **Concert Pharmaceuticals, Inc.,**  
Lexington, MA (US)(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.This patent is subject to a terminal dis-  
claimer.(21) Appl. No.: **14/518,254**(22) Filed: **Oct. 20, 2014**(65) **Prior Publication Data**

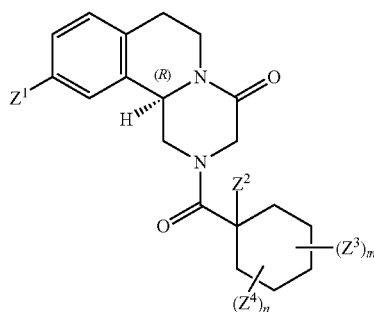
US 2015/0141431 A1 May 21, 2015

**Related U.S. Application Data**(63) Continuation of application No. 13/411,198, filed on  
Mar. 2, 2012, now Pat. No. 8,889,687.(60) Provisional application No. 61/599,147, filed on Feb.  
15, 2012, provisional application No. 61/449,312,  
filed on Mar. 4, 2011.(51) **Int. Cl.****C07D 241/38** (2006.01)**C07D 471/04** (2006.01)**C07B 59/00** (2006.01)**A61K 31/4184** (2006.01)**A61K 31/4985** (2006.01)(52) **U.S. Cl.**CPC ..... **C07D 471/04** (2013.01); **A61K 31/4184**  
(2013.01); **A61K 31/4985** (2013.01); **C07B**  
**59/002** (2013.01)(58) **Field of Classification Search**CPC ..... C07D 241/38  
USPC ..... 544/344  
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**4,001,411 A 1/1977 Seubert et al.  
6,221,335 B1 4/2001 Foster  
6,440,710 B1 8/2002 Keinan et al.  
6,603,008 B1 8/2003 Ando et al.  
7,517,990 B2 4/2009 Ito et al.  
8,563,554 B2 10/2013 Liu et al.  
8,889,687 B2 11/2014 Liu et al.  
2004/0198762 A1 10/2004 Naicker et al.  
2004/0253180 A1 12/2004 Foster et al.  
2007/0082929 A1 4/2007 Gant et al.**FOREIGN PATENT DOCUMENTS**WO 95/26325 A2 10/1995  
WO 2007118651 A1 10/2007  
WO 2010/107791 A2 9/2010**OTHER PUBLICATIONS**Andrews, P., et al., Praziquantel, Med Res Rev, (3):147-200, 1983.  
Avery, Mitchell A., et al., Deuterated Antimalarials: Synthesis of tri  
deutero-artemisinin, Dihydroartemisinin, and Arteether, Journal of  
Labelled Compounds and Radiopharmaceuticals 38(3):249-254,  
1996.  
Baille, T. A., "The Use of Stable Isotopes in Pharmacological  
Research," Pharmacological Reviews, 33(2): 81-132 (1981).  
Blake, Martin I., et al., Studies with Deuterated Drugs, Journal of  
Pharmaceutical Sciences, 64(3):367-391; 1975.

(Continued)

*Primary Examiner* — Douglas M Willis(74) *Attorney, Agent, or Firm* — McCarter & English, LLP;  
Steven G. Davis; Emily Dertz(57) **ABSTRACT**This invention in one embodiment is directed to a compound  
of Formula Ia;

Formula Ia

where the designation (R) indicates that the designated car-  
bon has the (R) stereochemistry; and wherein Z<sup>1</sup> is hydrogen  
or fluorine; Z<sup>2</sup> is hydrogen, deuterium, or fluorine; Z<sup>3</sup> is deu-  
terium; Z<sup>4</sup> is fluorine; m is an integer from 0 to 10; n is an  
integer from 0 to 2; provided that: the sum of m+n does not  
exceed 10; and when both Z<sup>1</sup> and Z<sup>2</sup> are hydrogen, the sum of  
m+n is greater than 0, and pharmaceutically acceptable salts  
thereof. This invention also provides compositions compris-  
ing one or more compounds of this invention and a carrier and  
the use of the disclosed compounds and compositions in  
methods of treating diseases and conditions that are benefi-  
cially treated by administering an antihelminthic agent, such as  
praziquantel.**21 Claims, No Drawings**

(56)

**References Cited****OTHER PUBLICATIONS**

Botros, Sanaa, et al., Comparative Efficacy and Bioavailability of Different Praziquantel Brands, *Experimental Parasitology*, 127:515-521, 2011.

Browne, T. R., "Stable Isotope Techniques in Early Drug Development: An Economic Evaluation," *J. Clin. Pharmacol.*, 38: 213-220 (1998).

Cherrah, Y., et al., "Study of Deuterium Isotope Effects on Protein Binding by Gas Chromatography/Mass Spectrometry. Caffeine and Deuterated Isotopomers," *Biomedical and Environmental Mass Spectrometry*, 14: 653-657 (1987).

Dayan, A.D., Albendazole, Mebendazole and Praziquantel. Review of Non-Clinical Toxicity and Pharmacokinetics, *Acta Tropica*, 86:141-159, 2003.

Dong, Yuxiang et al., Praziquantel Analogs with Activity Against Juvenile *Schistosoma mansoni*, *Bioorganic & Medicinal Chemistry Letters*, 20(8):2481-2484, 2010.

Dourish, C.T., et al., Potentiation of the Behavioural Effects of the Antidepressant Phenelzine by Deuterium Substituted; *Psychopharmacology*, Springer Verlag, 81:122-125, Jan. 1, 1983.

Dyck, L. E., et al., "Effects of Deuterium Substitution on the Catabolism of ?-Phenylethylamine: An In Vivo Study," *Journal of Neurochemistry*, 46(2): 399-404 (1986).

Dömling, Alexander, et al., Praziquantel and Schistosomiasis, *ChemMedChem*, 5:1420-1434, 2010.

Fisher, M.B. et al., "The Complexities Inherent in Attempts to Decrease Drug Clearance by Blocking Sites of CYP-Mediated Metabolism," *Curr. Opin. Drug Discov. Devel.*, 9(1):101-109 (2006).

Foster, A. B., "Deuterium Isotope Effects in Studies of Drug Metabolism," *Trends in Pharmacological Sciences*, 5: 524-527 (1984).

Foster, A. B., "Deuterium Isotope Effects in the Metabolism of Drugs and Xenobiotics: Implications for Drug Design," *Advances in Drug Research*, 14: 1-40 (1985).

Gouyette, A., "Synthesis of Deuterium-labelled Elliptinium and its Use in Metabolic Studies," *Biomedical and Environmental Mass Spectrometry*, 15: 243-247 (1988).

Haskins, N. J., "The Application of Stable Isotopes in Biomedical Research," *Biomedical Mass Spectrometry*, 9(7): 269-277 (1982).

Hong, Sung-Tae, et al., Sustained-Release Praziquantel Tablet: Pharmacokinetics and the Treatment of Clonorchiasis in Beagle Dogs, *Parasitol Res*, 91:316-320; 2003.

Honma S., et al., "The Metabolism of Roxatidine Acetate Hydrochloride," *Drug Metabolism and Disposition*, 15(4): 551-559 (1987).

Huang, J. et al., Metabolite Profiling of Praziquantel and its Analogs During the Analysis of in vitro Metabolic Stability Using Information-Dependent Acquisition on a Hybrid Triple Quadrupole Linear Ion Trap Mass Spectrometer, *Drug Metab. Pharmacokinet.* 25 (5): 487-499 2010.

International Search Report of PCT/US2012/27528, Jun. 12, 2012.

International Search Report of PCT/US2010/027476, Sep. 27, 2010.  
Kushner, D.J. et al., "Pharmacological Uses and Perspectives of Heavy Water and Deuterated Compounds," *Can. J. Physiol. Pharmacol.*, 77:79-88 (1999).

Lerch, C. et al., Investigation of the stereoselective metabolism of praziquantel after incubation with rat liver microsomes by capillary electrophoresis and liquid chromatography-mass spectrometry, *Journal of Chromatography B*, 708 267-275, 1998.

Li, Rongshi, et al., Racemization of Vinylglycolate Catalyzed by Mandelate Racemase, *J. Org. Chem.*, 60:3347-3351, 1995.

Li, Xue-Qing, et al., Identification of Human Cytochrome P450s that Metabolise Anti-Parasitic Drugs and Predictions of In Vivo Drug Hepatic Clearance from In Vitro Data; *Eur J Clin Pharmacol*, 59:429-442; 2003.

Maltais, F., In Vitro and In Vivo Isotope Effects with Hepatitis C Protease Inhibitors: Enhanced Plasma Exposure of Deuterated Telaprevir versus Telaprevir in Rats; *J. Med. Chem.*, 52:7993-8001, 2009.

Masimirembwa, Collen M., et al., Characterisation of Praziquantel Metabolism by Rat Liver Microsomes Using cytochrome P450 Inhibitors, *Biochemical Pharmacology*, 48(9); 1779-1783, 1994.

Park, B. Kevin, et al., Metabolism of Fluorine-Containing Drugs, *Annu. Rev. Pharmacol. Toxicol.*; 41:443-70; 2001.

Pieniaszek, H. J., et al., "Moricizine Bioavailability via Simultaneous, Dual, Stable Isotope Administration: Bioequivalence Implications," *J. Clin. Pharmacol.*, 39: 817-825 (1999).

Ridititid, Wibool, et al., Rifampin Markedly Decreases Plasma Concentrations of Praziquantel in Healthy Volunteers, *Clinical Pharmacology & Therapeutics*, 72(5):505-513, 2002.

Shu-Hua, Xiao, et al., Plasma Pharmacokinetics and Therapeutic Efficacy of Praziquantel and 4-Hydroxypraziquantel in *Schistosoma japonicum*-Infected Rabbits After Oral, Rectal, and Intramuscular Administration; *Am J. Trop. Med. Hyg.* 46(5):582-588; 1992.

Tonn G. R., et al., "Simultaneous Analysis of Diphenhydramine and a Stable Isotope Analog (2H10) Diphenhydramine Using Capillary Gas Chromatography with Mass Selective Detection in Biological Fluids from Chronically Instrumented Pregnant Ewes," *Biological Mass Spectrometry*, 22: 633-642 (1993).

Wolen, R. L., "The Application of Stable Isotopes to Studies of Drug Bioavailability and Bioequivalence," *J. Clin. Pharmacol.*, 26: 419-424 (1986).

Written Opinion of PCT/US2010/027476, Sep. 20, 2010.

Fukuto, J. M., et al. "Determination of the mechanism of demethylenation of (methylenedioxy) phenyl compounds by cytochrome P450 using deuterium isotope effects." *Journal of medicinal chemistry* 34.9 (1991): 2871-2876.

Roszkowski, et al., *Tetrahedron Asymmetry*, 17, 2006, 1415-1419.

Biltricide®, FDA Label, 2011.

1

# METHODS OF USE COMPRISING DEUTERATED PYRAZINO[2,1-A]ISOQUINOLINES

## RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/411,198, filed Mar. 2, 2012 (now U.S. Pat. No. 8,889,687). U.S. application Ser. No. 13/411,198 claims the benefit of U.S. Provisional Patent Application No. 61/449,312, filed Mar. 4, 2011 and U.S. Provisional Patent Application No. 61/599,147, filed Feb. 15, 2012. The contents of the foregoing applications are each incorporated herein by reference.

## BACKGROUND OF THE INVENTION

Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use or limit their use in certain indications. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment. A rapidly metabolized drug may also expose patients to undesirable toxic or reactive metabolites.

Another ADME limitation that affects many medicines is the formation of toxic or biologically reactive metabolites. As a result, some patients receiving the drug may experience toxicities, or the safe dosing of such drugs may be limited such that patients receive a suboptimal amount of the active agent. In certain cases, modifying dosing intervals or formulation approaches can help to reduce clinical adverse effects, but often the formation of such undesirable metabolites is intrinsic to the metabolism of the compound.

In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, D. J. et al., Antimicrobial agents and chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6 metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al., Clinical Pharmacology and Therapeutics, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at [www.accessdata.fda.gov](http://www.accessdata.fda.gov)).

In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme's activity can affect the metabolism and clearance of other drugs metabolized by that

2

same enzyme. CYP inhibition can cause other drugs to accumulate in the body to toxic levels.

A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug or to reduce the formation of undesirable metabolites by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Compared to hydrogen, deuterium forms stronger bonds with carbon. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, M I et al, J Pharm Sci, 1975, 64:367-91; Foster, A B, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, D J et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, M B et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 ("Fisher")). The results have been variable and unpredictable. For some compounds deuteration caused decreased metabolic clearance in vivo. For others, there was no change in metabolism. Still others demonstrated increased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism (see Foster at p. 35 and Fisher at p. 101).

The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its non-deuterated counterpart. See, for example, Fukuto et al. (J. Med. Chem. 1991, 34, 2871-76). Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

Praziquantel, also known as 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one, acts as an antihelminthic agent through mechanisms as yet unproven, although experimental evidence indicates that praziquantel increases the permeability of parasitic cell membranes to calcium ions, thereby inducing contraction of the parasites. The drug, sold as Biltricide, further causes vacuolization and disintegration of the parasite tegument. (See FDA label for BILTRICIDE® at <http://www.fda.gov/cder/foi/label/2004/18714s008,009lbl.pdf>) (last visited Feb. 2, 2009)).

Praziquantel is currently approved for the treatment of infections due to all species of *Schistosoma* (e.g. *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*)—see, e.g., The Lancet, Volume 376, Issue 974, Pages 496-498, 14 Aug. 2010.—and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini* and is currently in clinical trials for the treatment of cysticercosis, neurocysticercosis (NCC), and malaria. Praziquantel is also useful for the treatment of indications that may be treated with anthelmintics, antischistosomal and anti-trematodes, according to [http://www.who.int/selection\\_medicines/committees/expert/17/sixteenth\\_adult\\_list\\_en](http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en)

.pdf (accessed February 2011). Praziquantel is also useful for the treatment of fascioliasis, paragonimiasis, tapeworms and cestodes, including: Echinococcosis; Cysticercosis, though it has been judged less effective than albendazole in treatment of neurocysticercosis; and intestinal tapeworms, according to <http://en.wikipedia.org/wiki/Praziquantel> (accessed February 2011). According to [http://www.dr.fostersmith.com/Rx-Info\\_Sheets/rx\\_praziquantel.pdf](http://www.dr.fostersmith.com/Rx-Info_Sheets/rx_praziquantel.pdf), praziquantel is also useful in veterinary medicine, for example in dogs for the removal of tapeworm. It is also useful in dogs in combination with pyrantel pamoate and febantel for the removal of hookworms, roundworms, and whipworms. As another example, praziquantel is useful in cats for the removal of tapeworm, and in combination with pyrantel pamoate also for the removal of various types of hookworms and roundworms. As another example, praziquantel is useful in ferrets, birds, chinchillas, mice, rats, hamsters, gerbils, and guinea pigs for the removal of tapeworms. As another example, praziquantel is useful in reptiles for the removal of tapeworms and flukes. A product containing praziquantel and pyrantel pamoate is Drontal®, which, according to <http://www.drugs.com/vet/drontal-praziquantel-pyrantel-pamoate-tablets.html> will remove tapeworms (*Dipylidium caninum*, *Taenia taeniaeformis*), hookworms (*Ancylostoma tubaeforme*), and large roundworms (*Toxocara cati*) in cats and kittens.

According to Meyer T, et al. (2009) "Taste, A New Incentive to Switch to (R)-Praziquantel in Schistosomiasis Treatment." *PLoS Negl Trop Dis* 3(1): e357. doi:10.1371/journal.pntd.0000357, the enantiomer of praziquantel having the (R) configuration is the enantiomer that has schistosomicidal activity. The (R) enantiomer has the additional advantage of having a significantly less bitter taste than racemic praziquantel.

Approximately 80% of a dose of praziquantel is excreted in the kidneys, almost exclusively (>99%) in the form of metabolites. (See FDA label for BILTRICIDE® @ <http://www.fda.gov/cder/foi/label/2004/18714s008,0091b1.pdf>). The main metabolic pathway in humans involves CYP 2B1 and CYP 3A4 mediated hydroxylation of praziquantel to the active (in vitro) metabolite, 4'-hydroxypraziquantel (as a mixture of cis and trans). Because 4'-hydroxypraziquantel is poorly taken-up by parasites in animal models, it is unlikely to contribute to efficacy in vivo. Additional metabolites include CYP mediated hydroxylation of the parent to 8-hydroxypraziquantel, and other unidentified mono- and di-hydroxylated forms of the parent drug (Godawska-Matysik, A et al., *Acta Pol Pharm*, 2006 September-October, 63(5):381-5).

Adverse events due to treatment with praziquantel are usually mild and transient and do not require treatment. These effects include the following, generally listed in order of severity: malaise, headache, dizziness, abdominal discomfort with or without nausea, rise in temperature and, rarely, urticaria. Such symptoms may also result from the infection itself and may be more frequent and/or serious in patients with a heavy worm burden. Due to drug-drug interactions, recommendations exist for co-dosing various drugs with praziquantel. Concomitant administration of drugs that increase the activity of drug metabolizing liver enzymes (Cytochrome P450), e.g. antiepileptic drugs (phenytoin, phenobarbital and carbamazepine), dexamethasone, may reduce plasma levels of praziquantel. Concomitant administration of rifampin should be avoided. Concomitant administration of drugs that decrease the activity of drug metabolizing liver enzymes (Cytochrome P 450), e.g. cimetidine, ketoconazole, itraconazole, erythromycin may increase plasma levels of praziquantel. Chloroquine, when taken simultaneously, may lead to lower concentrations of praziquantel in blood. The mechanism of

this drug-drug interaction is unclear. (see <http://www.fda.gov/cder/foi/label/2004/18714s008,0091b1.pda> (last visited Feb. 20, 2009))

Despite the beneficial activities of Praziquantel, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

## SUMMARY OF THE INVENTION

This invention relates to novel compounds that are pyrazinoisoquinoline derivatives, and pharmaceutically acceptable salts thereof. More specifically, this invention relates to novel pyrazinoisoquinoline derivatives that are derivatives of praziquantel. This invention also provides compositions comprising one or more compounds of this invention and a carrier and the use of the disclosed compounds and compositions in methods of treating diseases and conditions that are beneficially treated by administering an antihelminthic agent, such as praziquantel.

## DETAILED DESCRIPTION OF THE INVENTION

The terms "ameliorate" and "treat" are used interchangeably and include both therapeutic treatment and prophylactic treatment (reducing the likelihood of development). Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

"Disease" means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of praziquantel will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada E et al., *Seikagaku* 1994, 66:15; Gannes L Z et al., *Comp Biochem Physiol Mol Integr Physiol* 1998, 119:725.

In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as "D" or "deuterium", the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least

5

6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

The term "isotopologue" refers to a species in which the chemical structure differs from a specific compound of this invention only in the isotopic composition thereof.

The term "compound," when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound. However, as set forth above the relative amount of such isotopologues in toto will be less than 49.9% of the compound. In other embodiments, the relative amount of such isotopologues in toto will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

The invention also provides salts of the compounds of the invention.

A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A "pharmaceutically acceptable counterion" is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate,  $\beta$ -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other

6

salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

The compounds of the present invention, may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention will include both racemic mixtures, and also individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, in certain embodiments less than 10% of other stereoisomers, in certain more specific embodiments less than 5% of other stereoisomers and in certain yet more specific embodiments less than 2% of other stereoisomers. Methods of obtaining or synthesizing an individual enantiomer for a given compound are well known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

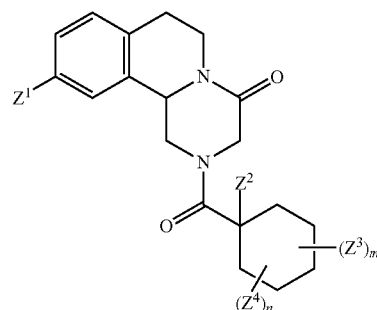
The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

"D" and "d" both refer to deuterium. "Stereoisomer" refers to both enantiomers and diastereomers. "Tert", "t", and "t-" each refer to tertiary. "US" refers to the United States of America.

Throughout this specification, a variable may be referred to generally (e.g., "each R") or may be referred to specifically (e.g.,  $R^1$ ,  $R^2$ ,  $R^3$ , etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

#### Therapeutic Compounds

The present invention in one embodiment provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

$Z^1$  is hydrogen or fluorine;

$Z^2$  is hydrogen, deuterium, or fluorine;

$Z^3$  is deuterium;

7

$Z^4$  is fluorine;

m is an integer from 0 to 10;

n is an integer from 0 to 2;

provided that:

the sum of m+n does not exceed 10; and

when both  $Z^1$  and  $Z^2$  are hydrogen, the sum of m+n is greater than 0.

In one embodiment, the invention provides a compound of Formula I, wherein:

m is 0, 2, 4, 6, 8, or 10; and

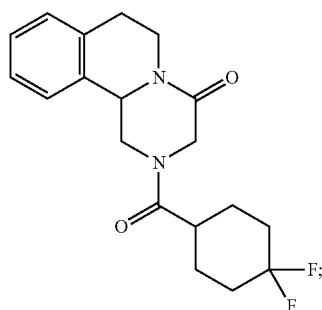
n is 0 or 2.

In another embodiment, the invention provides a compound of Formula I, wherein for each  $Z^3$  that is present, there is another  $Z^3$  present which is attached to the same carbon. In an example of this embodiment, m is 10 and  $Z^2$  is hydrogen. In another example of this embodiment, m is 10 and  $Z^2$  is deuterium. In an example of this embodiment, m is 2, wherein the carbon bearing the two deuterium atoms is the carbon in the 4-position relative to the carbon attached to the C=O group; n is 0; and  $Z^2$  is hydrogen. In another example of this embodiment, m is 2, wherein the carbon bearing the two deuterium atoms is the carbon in the 4-position relative to the carbon attached to the C=O group; n is 0; and  $Z^2$  is deuterium. In an example of this embodiment, m is 6, wherein the three carbons each bearing two deuterium atoms are the carbons in the 3-position, in the 4-position, and in the 5-position relative to the carbon attached to the C=O group; n is 0; and  $Z^2$  is hydrogen. In another example of this embodiment, m is 6, wherein the three carbons each bearing two deuterium atoms are the carbons in the 3-position, in the 4-position, and in the 5-position relative to the carbon attached to the C=O group; n is 0; and  $Z^2$  is deuterium. In one aspect of the embodiments wherein m is 6, the isotopic enrichment factor is at least 6000 (90% deuterium incorporation), 6333.3 (95% deuterium incorporation), such as at least 6466.7 (97% deuterium incorporation).

In another embodiment, the invention provides a compound of Formula I, wherein for each  $Z^4$  that is present, there is another  $Z^4$  present which is attached to the same carbon.

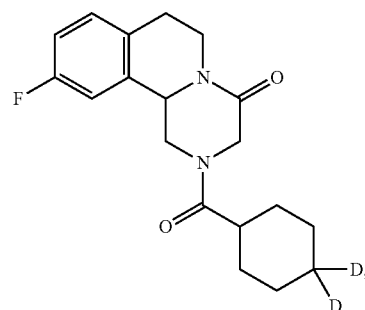
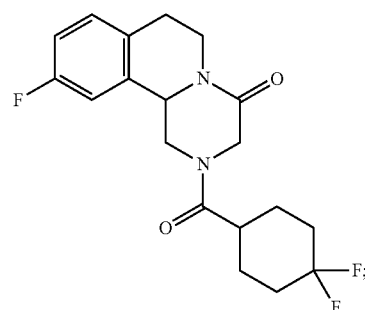
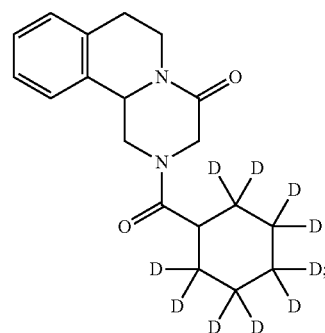
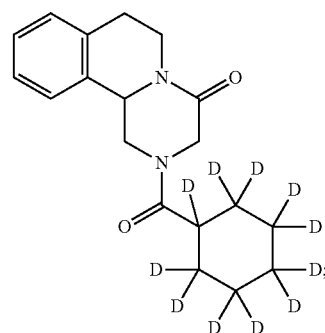
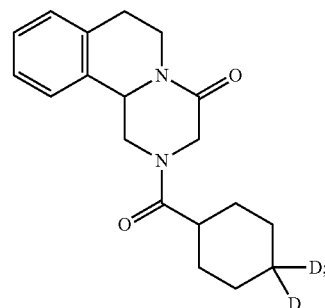
In another embodiment, the invention provides a compound of Formula I, wherein  $Z^2$  is hydrogen.

In yet another embodiment, the compound is selected from any one of the following compounds:



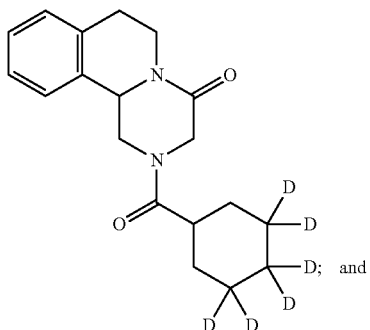
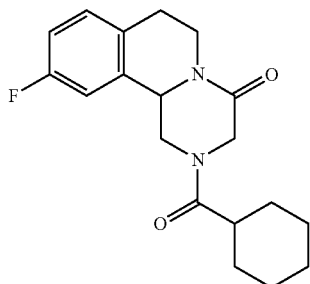
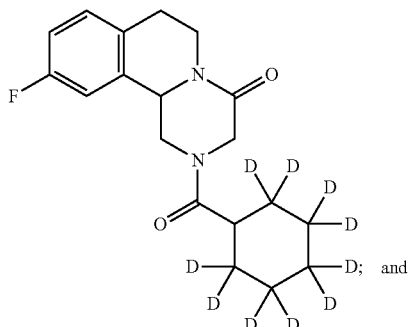
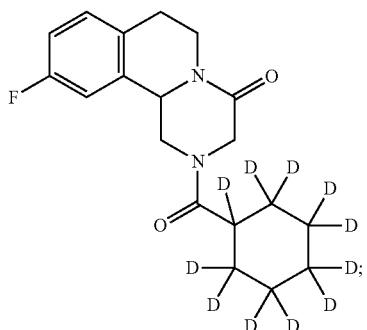
8

-continued



9

-continued

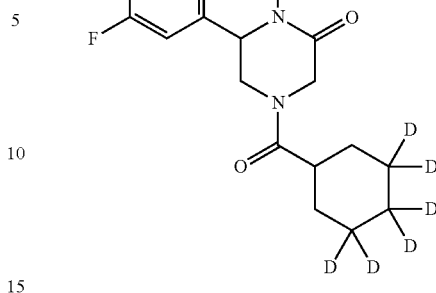


10

-continued

106

110

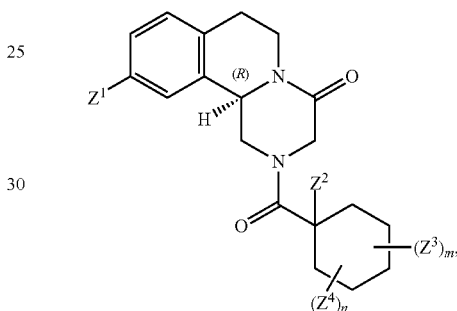


or a pharmaceutically acceptable salt thereof.

In one embodiment the compound of Formula I is a compound of Formula Ia:

Formula Ia

Ia



where the designation (R) indicates that the designated carbon has the (R) stereochemistry; or a pharmaceutically acceptable salt thereof, wherein:

$Z^1$  is hydrogen or fluorine;

$Z^2$  is hydrogen, deuterium, or fluorine;

$Z^3$  is deuterium;

$Z^4$  is fluorine;

$m$  is an integer from 0 to 10;

$n$  is an integer from 0 to 2;

provided that:

the sum of  $m+n$  does not exceed 10; and

when both  $Z^1$  and  $Z^2$  are hydrogen, the sum of  $m+n$  is greater than 0.

In one embodiment of Formula Ia,

$m$  is 0, 2, 4, 6, 8, or 10; and

$n$  is 0 or 2.

In another embodiment of Formula Ia, for each  $Z^3$  that is present, there is another  $Z^3$  present which is attached to the same carbon. In an example of this embodiment,  $m$  is 10 and  $Z^2$  is hydrogen. In another example of this embodiment,  $m$  is 10 and  $Z^2$  is deuterium. In an example of this embodiment,  $m$  is 2, wherein the carbon bearing the two deuterium atoms is the carbon in the 4-position relative to the carbon attached to the  $C=O$  group;  $n$  is 0; and  $Z^2$  is hydrogen. In another example of this embodiment,  $m$  is 2, wherein the carbon bearing the two deuterium atoms is the carbon in the 4-position relative to the carbon attached to the  $C=O$  group;  $n$  is 0; and  $Z^2$  is deuterium. In an example of this embodiment,  $m$  is 6, wherein the three carbons each bearing two deuterium atoms are the carbons in the 3-position, in the 4-position, and in the 5-position relative to the carbon attached to the  $C=O$

## 11

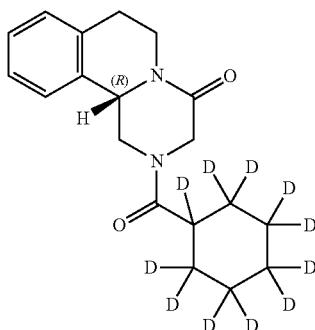
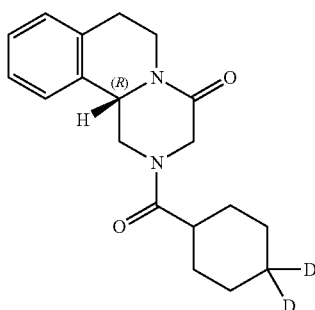
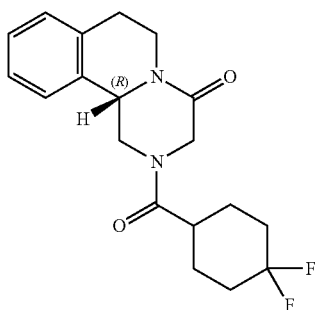
group;  $n$  is 0; and  $Z^2$  is hydrogen. In another example of this embodiment,  $m$  is 6, wherein the three carbons each bearing two deuterium atoms are the carbons in the 3-position, in the 4-position, and in the 5-position relative to the carbon attached to the  $C=O$  group;  $n$  is 0; and  $Z^2$  is deuterium. In one aspect of the embodiments wherein  $m$  is 6, the isotopic enrichment factor is at least 6000 (90% deuterium incorporation), 6333.3 (95% deuterium incorporation), such as at least 6466.7 (97% deuterium incorporation).

In another embodiment of Formula Ia, for each  $Z^4$  that is present, there is another  $Z^4$  present which is attached to the same carbon.

In another embodiment of Formula Ia,  $Z^2$  is hydrogen.

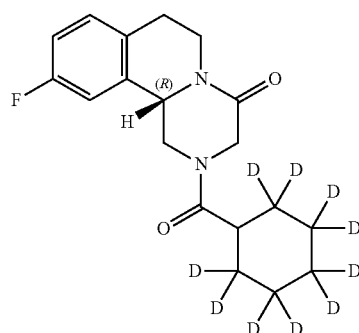
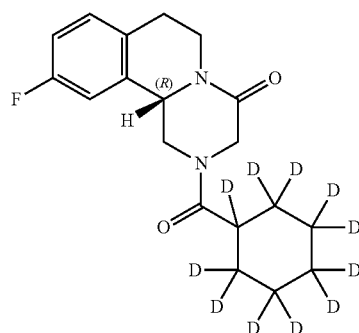
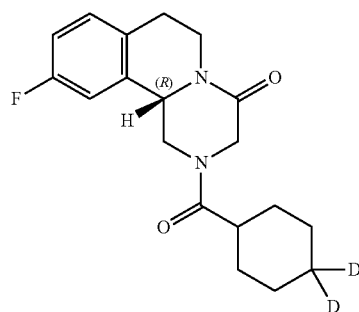
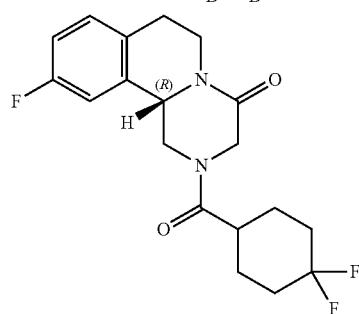
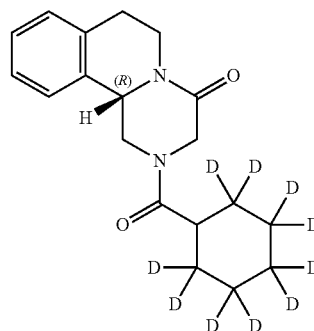
In another embodiment of Formula Ia,  $Z^2$  is deuterium.

In yet another embodiment, the compound of Formula Ia is selected from any one of the following compounds:



## 12

-continued



103(a)

100(a)

105(a)

101(a)

106(a)

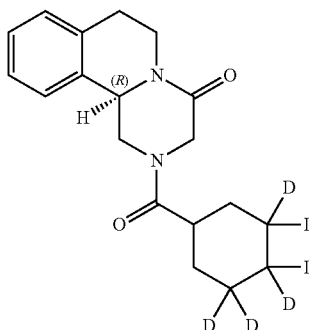
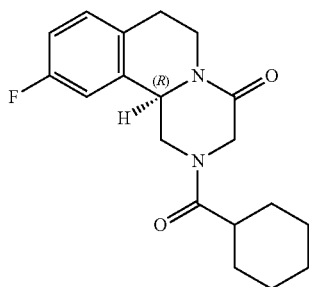
102(a)

107(a)

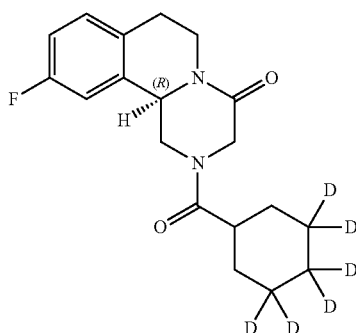


**13**

-continued



and



or a pharmaceutically acceptable salt thereof.

In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

The synthesis of compounds of Formula I and Formula Ia can be readily achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance, in:

Kim, Joong Hyup; Lee, Yong; Park, Hokoon; Kim, Choong. Tetrahedron (1998), 54(26):7395-7400.

Shan, Yuhua; Lin, Furong; Yuan, Shunfu; Xu, Ping. Faming Zhuanli Shenqing Gongkai Shuomingshu (2005), Chinese Patent Publication CN100503582.

El-Fayyomy, Shaimaa; Mansour, Wafaa; Todd, Matthew H. Tetrahedron Letters (2006), 47(8): 1287-1290.

Todd, Matthew H.; Ndubaku, Chudi; Bartlett, Paul A. Journal of Organic Chemistry (2002), 67(12):3985-3988.

Kim, Joong Hyup; Lee, Yong; Kim, Choong. Heterocycles (1998), 48(11):2279-2285.

Sergovskaya, N. L.; Chernyak, S. A.; Shekhter, O. V.; Tsizin, Yu. S. Khimiya Geterotsiklicheskikh Soedinenii (1991), 8:1107-9.

Yuste, Francisco; Pallas, Yadira; Barrios, Hector; Ortiz, Benjamin; Sanchez-Obregon, Ruben. Journal of Heterocyclic Chemistry (1986), 23(1):189-90.

Berkowitz, William F.; John, Thomas V. Journal of Organic Chemistry (1984), 49(26):5269-71.

**14**

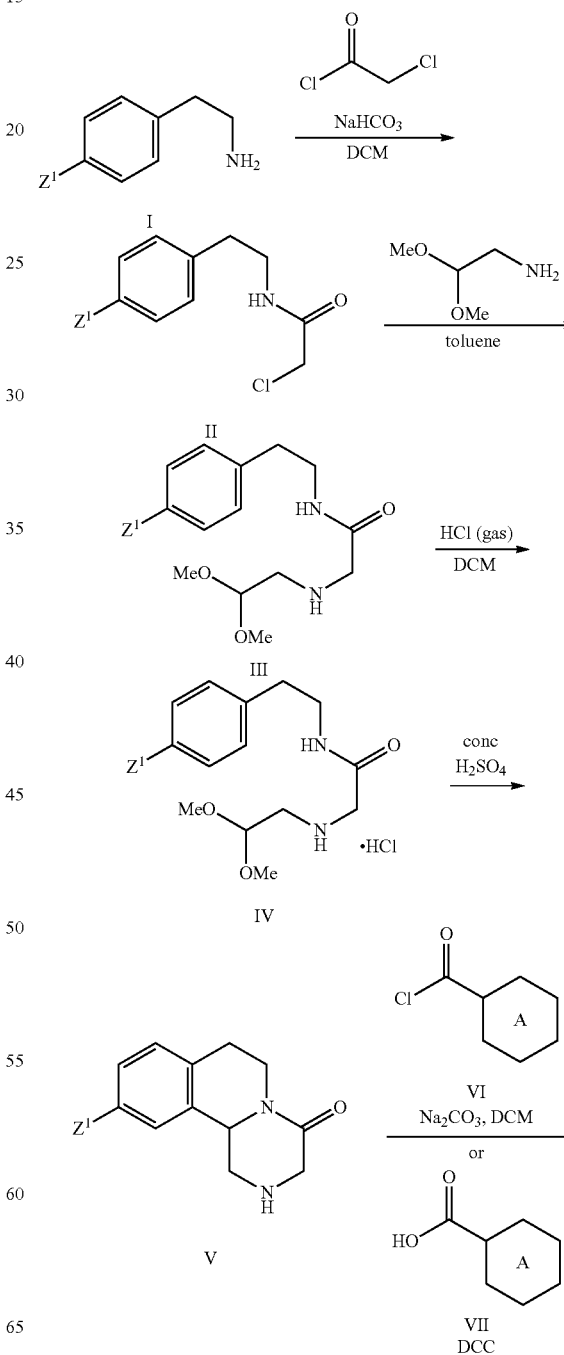
Frehel, Daniel; Maffrand, Jean Pierre. Heterocycles (1983), 20(9):1731-5.

Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

#### Exemplary Synthesis

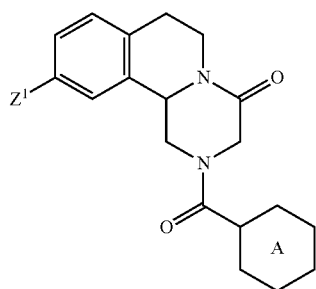
A convenient method for synthesizing compounds of Formula I is depicted in Scheme 1.

Scheme 1: Method for Preparing Compounds of Formula I



15

-continued

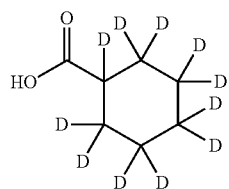


Formula I

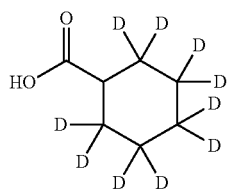
As described in the literature cited above and depicted in Scheme 1, a substituted benzylamine 1 is acylated with 2-chloroacetyl chloride to afford chloride II. Chloride II is treated with 2,2-dimethoxyethanamine to provide acetal III. Formation of the HCl salt IV, followed by cyclization in the presence of concentrated sulfuric acid, affords tricycle V. Acylation with either acyl chlorides VI in the presence of sodium carbonate or in the presence of triethylamine, or carboxylic acids VII in the presence of a coupling agent such as dicyclohexyl carbodiimide (DCC) provides compounds of Formula I. In Scheme 1, Z<sup>1</sup> is as defined for a compound of Formula I.

Schemes 2-4 depict the preparation of exemplary carboxylic acids VIIb, VIIc and VIId which are useful reagents for Scheme 1. Scheme 5 depicts a convenient method for synthesizing intermediates of Formula Va for use in preparing compounds of Formula Ia.

Scheme 2: Method for Preparation of Intermediate VIIb



VIIa

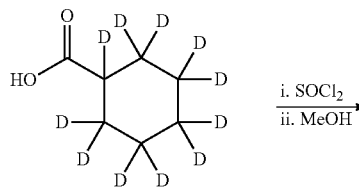


VIIb

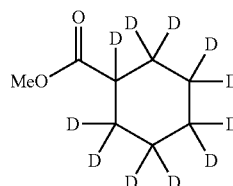
As depicted in Scheme 2, commercially-available cyclohexanecarboxylic-d11 acid VIIa is treated with HCl to afford exchanged carboxylic acid VIIb.

16

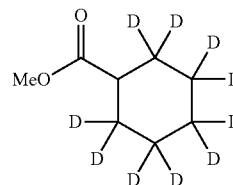
Scheme 2a: Alternative Method for Preparation of Intermediate VIIb:



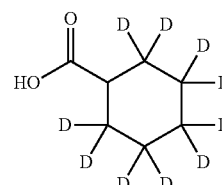
VIIa



XIa



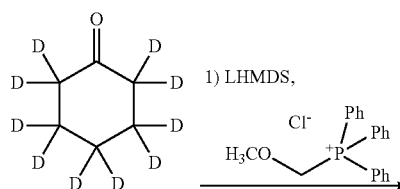
XIb



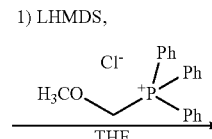
VIIb

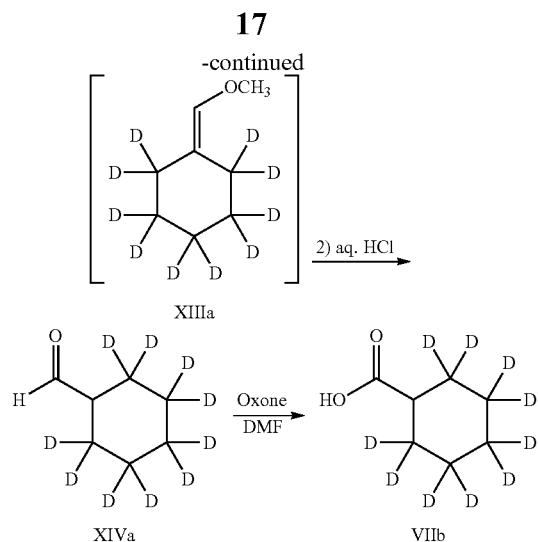
Alternatively, carboxylic acid VIIa may be converted to a methyl ester and treated with LDA (or NaOMe/MeOH), followed by ester hydrolysis to yield VIIb, in accordance with Scheme 2a.

Scheme 2b: Alternative Method for Preparation of Intermediate VIIb:



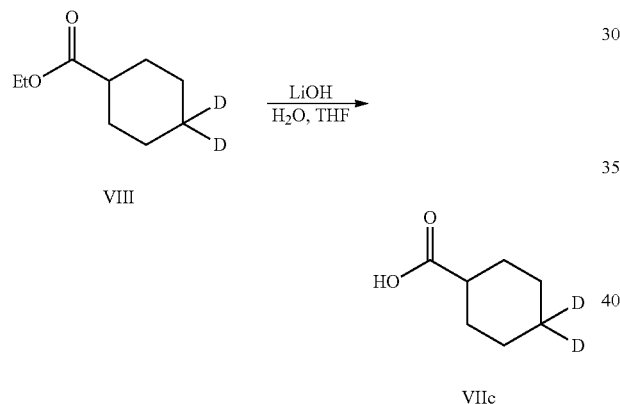
XIIa





As yet another alternative, commercially available ketone XIIa is converted to aldehyde XIVa via a Wittig reaction. The aldehyde is then oxidized with Oxone® reagent to yield VIIb, in accordance with Scheme 2b.

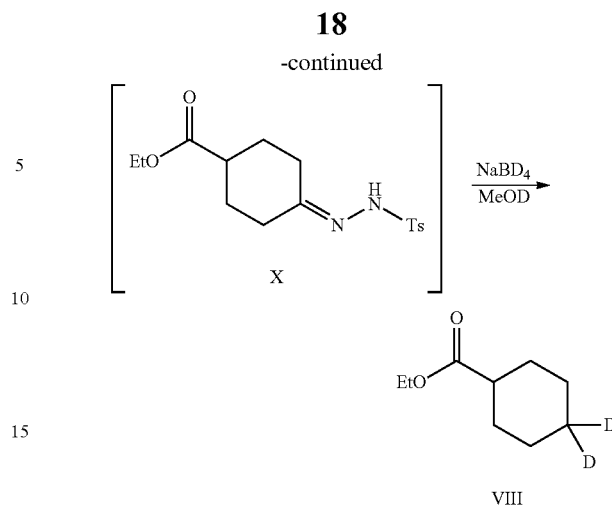
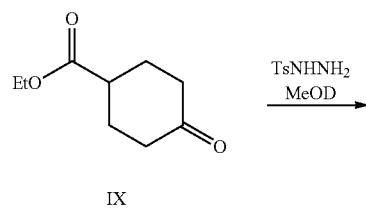
Scheme 3: Method for Preparation of Intermediate VIIc



Known cyclohexane-4,4-d2-carboxylic acid ethyl ester VIII [Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1995), (5), 527-35] is hydrolyzed to carboxylic acid VIIc, in accordance with Scheme 3, by treatment with lithium hydroxide in aqueous THF according to the method of Journal of Organic Chemistry, 58(23), 6255-65; 1993.

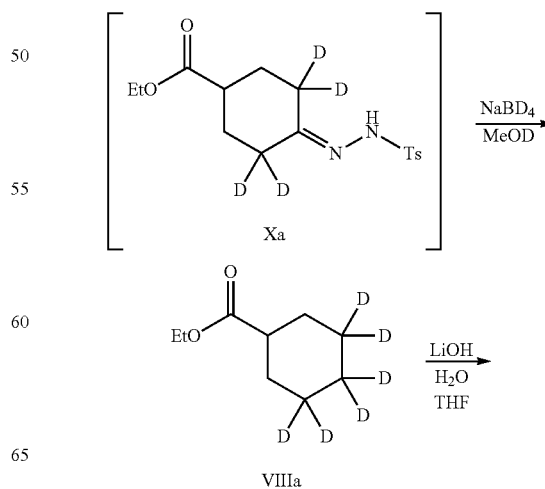
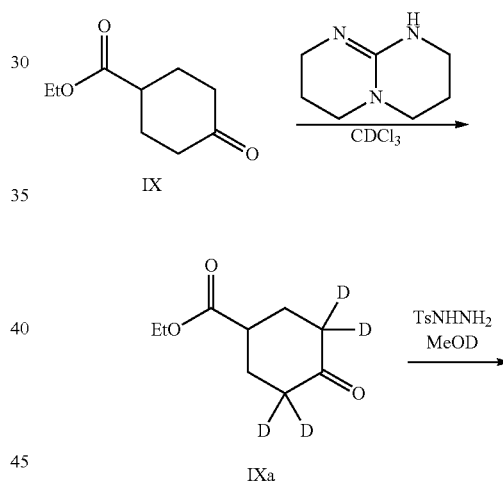
VIII in Scheme 3 may be prepared as shown in Scheme 3a below:

Scheme 3a: Method for Preparation of Intermediate VIII



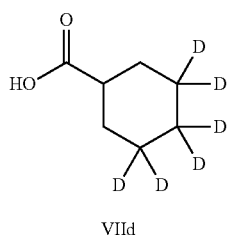
As shown in Scheme 3a, commercially available IX is treated with p-toluenesulfonyl hydrazide (TsNHNH<sub>2</sub>) to afford intermediate X, which is treated with sodium borodeuteride to provide VIII.

Scheme 4: Method for Preparation of Intermediate VIId:



19

-continued



As shown in Scheme 4, commercially available IX is subjected to hydrogen/deuterium exchange via treatment with 2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidine and  $\text{CDCl}_3$  to afford IXa. IXa is then treated with p-toluenesulfonyl hydrazide ( $\text{TsNHNH}_2$ ) to afford intermediate Xa, which is treated with sodium borodeuteride to provide VIIIa. Ester VIIIa is then hydrolyzed with  $\text{LiOH}$  to afford VIIId.

Table 1 summarizes commercially available starting materials and reagents useful for the preparation of compounds depicted in Scheme 1.

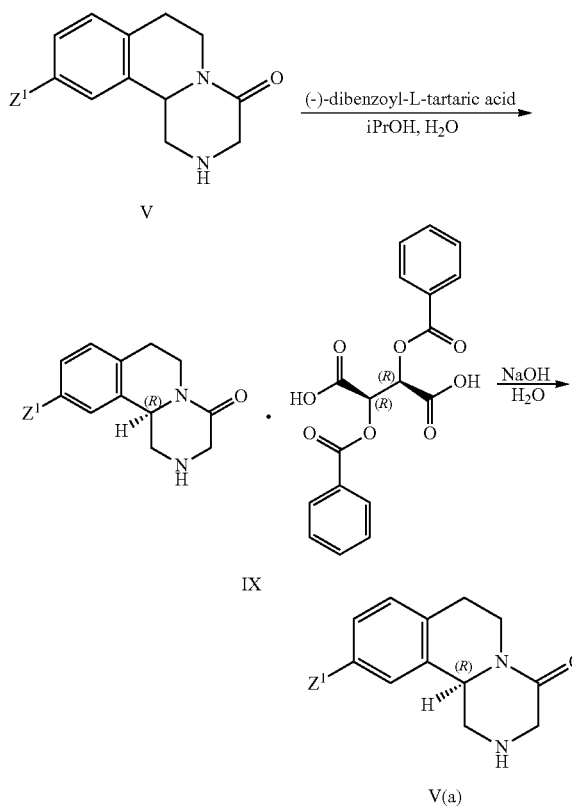
TABLE 1

Compound	Name
	4-Fluorophenethylamine
	2-Phenylethylamine
	4,4-Difluorocyclohexylcarboxylic acid
	Cyclohexanecarboxylic-d11 acid
	Cyclohexanecarbonyl chloride

A convenient method for synthesizing intermediates of Formula Va for use in preparing compounds of Formula Ia is depicted in Scheme 5.

20

Scheme 5: Method for the Preparation of Intermediates V(a)



As shown in Scheme 5, resolving amine V (prepared as disclosed in Scheme 1) via an intermediary salt IX provides R-enantiomer amine V(a) which may then be converted to the desired final products of Formula Ia via the methods indicated in Scheme 1 for the compounds of formula I. The chiral resolution of amine V is performed in a manner analogous to that described online at: [http://www.ourexperiment.org/rac-res\\_pzq/1309/Multigramscale\\_racemic\\_resolution\\_of\\_praziquanamine\\_with\\_DibenzoylLtartaric\\_acid\\_MW4913.html](http://www.ourexperiment.org/rac-res_pzq/1309/Multigramscale_racemic_resolution_of_praziquanamine_with_DibenzoylLtartaric_acid_MW4913.html) (accessed January 2011). In brief, V and (-)-dibenzoyl-L-tartaric acid are heated in aqueous iPrOH until a solution is formed. The solution is allowed to cool and the resulting salt precipitate is collected. The collected salt is recrystallized by heating in aqueous iPrOH until a solution is formed. The solution is allowed to cool and the resulting salt precipitate is collected. The mother liquor may be cooled further to facilitate collection of additional crops of salt precipitate. The isolated salt precipitate is suspended in water and the mixture is made basic by addition of aqueous  $\text{NaOH}$  to pH 11. The resulting aqueous solution is extracted with  $\text{CH}_2\text{Cl}_2$  to afford the free base V(a).

The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e.,  $Z^1$ ,  $Z^2$ ,  $Z^3$ , etc.) or not. The suitability of a chemical group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

Additional methods of synthesizing compounds of Formula I or Ia and their synthetic precursors, including those

within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, Comprehensive Organic Transformations, VCH Publishers (1989); Greene T W et al., Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and Paquette L, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

#### Compositions

The invention also provides pyrogen-free compositions comprising an effective amount of a compound of Formula I or Ia (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and an acceptable carrier. Preferably, a composition of this invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See "Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences)," David J. Hauss, ed. Informa Healthcare, 2007; and "Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples," Kishor M. Wasan, ed. Wiley-Interscience, 2006.

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Pat. No. 7,014,866; and United States patent publications 20060094744 and 20060079502.

The pharmaceutical compositions of a compound of Formula I or Ia, or a pharmaceutically acceptable salt thereof, include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the

formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, Md. (20th ed. 2000).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

23

For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz J D and Zaffaroni A C, U.S. Pat. No. 6,803,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics

24

in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the subject, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as Praziquantel. Such agents include those indicated as being useful in combination with Praziquantel, including but not limited to, those described in WO 2005055973, WO 2006061214, U.S. Pat. No. 4,303,659, U.S. Pat. No. 4,468,390, U.S. Pat. No. 4,447,414, WO 9505181, WO 9720567, WO 9806407, WO 2002094288, WO 2004006906, and WO 2006120495.

Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from infections due to all species of *Schistosoma* (e.g. *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini*; cysticercosis; neurocysticercosis (NCC); malaria; infection due to nematodes, sarcocystis, neosporosis or toxoplasmosis or isosporosis; animal infection or neoplasm of cerebrospinal tissue characterized by a risk of death; cancer; immune system dysfunction including HIV infection; parasitic infection of farm and domestic animals (pets) in the cases of cestodes, trematodoses, nematodoses and pests (ticks, mites and insects) invasions; parasitic diseases including toxoplasmosis, malaria, African trypanosomiasis, Chagas disease, leishmaniasis and schistosomiasis; helminthosis in domestic animals.

In one embodiment, the second therapeutic agent is selected from albendazole.

In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent

are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat (therapeutically or prophylactically) the target disorder. For example, an effective amount is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. In certain embodiments, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to therapeutically treat the target disorder.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother. Rep 50: 219. Body surface area may be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

In one embodiment, an effective amount of a compound of this invention can range from about 0.2 mg/kg of body weight to about 250 mg/kg of body weight per treatment. In more specific embodiments the range is from about 2 mg/kg to 125 mg/kg, or from about 4 mg/kg to 50 mg/kg, or most specifically from about 20 mg/kg to about 25 mg/kg or body weight per treatment. Treatment typically is administered three times daily for one day.

Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for praziquantel.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

## Methods of Treatment

In another embodiment, the invention provides a method of disrupting cell permeability to calcium ions in a parasitic cell, comprising contacting a cell with one or more compounds of Formula I or Ia herein.

According to another embodiment, the invention provides a method of treating a disease or condition in a patient in need thereof that is beneficially treated by praziquantel comprising the step of administering to said patient an effective amount of a compound or a composition of this invention, or a pharmaceutically acceptable salt of said compound. Such diseases and conditions are well known in the art and are disclosed in the following non-limited list of patents and published applications: U.S. Pat. No. 4,001,411, U.S. Pat. No. 4,362,875, JP 51082298, U.S. Pat. No. 4,303,659, WO 9505181, WO 9720567, WO 2001089497, US 2003022879, WO 2004006906, WO 2004047842, and WO 2007012180. Such diseases include, but are not limited to, infections due to all species of *schistosoma* (e.g. *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini*; cysticercosis; neurocysticercosis (NCC); malaria; infection due to nematodes, sarcocystis, neosporosis or toxoplasmosis or isosporosis; animal infection or neoplasm of cerebrospinal tissue characterized by a risk of death; cancer; immune system dysfunction including HIV infection; parasitic infection of farm and domestic animals (pets) in the cases of cestodes, trematodes, nematodes and pests (ticks, mites and insects) invasions; parasitic diseases including toxoplasmosis, malaria, African trypanosomiasis, Chagas disease, leishmaniasis and schistosomiasis; and helminthosis in domestic animals. Such indications also include fascioliasis, paragonimiasis, tapeworms and cestodes, including: Echinococcosis; Cysticercosis; and intestinal tapeworms.

In one particular embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof selected from infections due to all species of *schistosoma* (e.g. *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini*; cysticercosis; neurocysticercosis (NCC); and malaria.

In another particular embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof selected from infections due to all species of *schistosoma* (e.g. *Schistosoma mekongi*, *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma hematobium*), and infections due to the liver flukes, *Clonorchis sinensis*/*Opisthorchis viverrini*.

In one embodiment, the method is a method for the treatment of a disease or condition selected from indications that may be treated with anthelmintics, antischistosomes and antitrematodes. In one embodiment, the method is a method for the treatment of fascioliasis, paragonimiasis, tapeworms and cestodes, including: Echinococcosis; Cysticercosis; and intestinal tapeworms. In one embodiment, the method is a method for (a) the removal of tapeworm in dogs; (b) in combination with pyrantel pamoate and febantel, for the removal of hookworms, roundworms, and whipworms in dogs; (c) the removal of tapeworm in cats; (d) in combination with pyrantel pamoate, the removal of hookworms and roundworms in cats; (e) the removal of tapeworms in ferrets, birds, chinchillas, mice, rats, hamsters, gerbils, or guinea pigs; (f) the removal of tapeworms and flukes in reptiles.

Methods delineated herein also include those wherein the patient is identified as in need of a particular stated treatment.

27

Identifying a patient in need of such treatment can be in the judgment of a patient or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In another embodiment, any of the above methods of treatment comprises the further step of co-administering to said patient one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with praziquantel. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent.

In particular, the combination therapies of this invention include co-administering a compound of Formula I or Ia, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent for treatment of the following conditions (with the particular second therapeutic agent indicated in parentheses following the indication): neurocysticercosis (albendazole), and malaria (albendazole).

The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of Formula I or Ia, or a pharmaceutically acceptable salt thereof, and a second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of Formula I or Ia, or a pharmaceutically acceptable salt thereof; and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said patient at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., *Pharmacotherapy Handbook*, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); *PDR Pharmacopoeia*, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

In one embodiment, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In yet another aspect, the invention provides a compound of Formula I or Ia, or a pharmaceutically acceptable salt thereof, alone or together with one or more of the above-

28

described second therapeutic agents for use in the treatment or prevention in a patient of a disease, disorder or symptom thereof delineated herein.

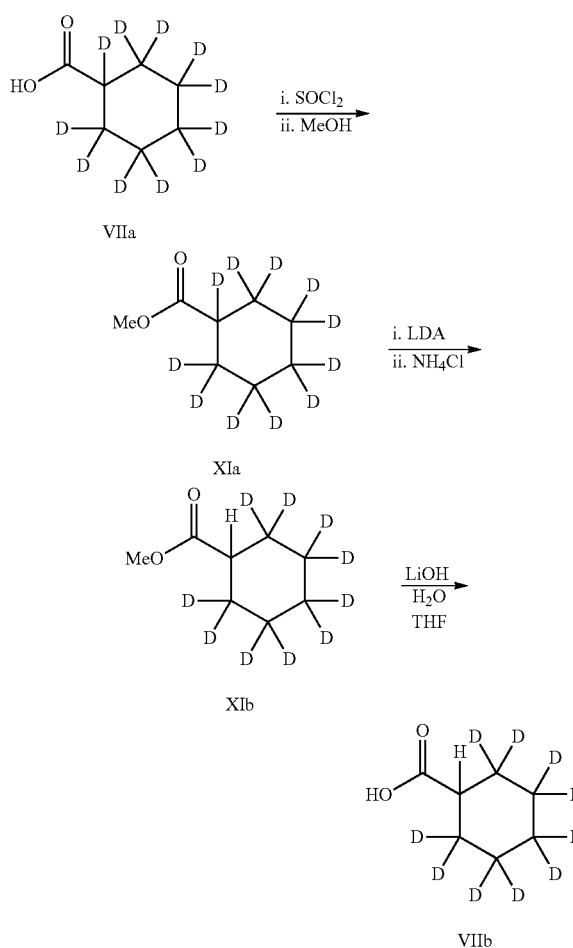
## EXAMPLES

## Example 1

Synthesis of  
2,2,3,3,4,4,5,5,6,6-d10-Cyclohexanecarboxylic acid  
(VIIb)

Intermediate VIIb was prepared as outlined in Scheme 6 below.

Scheme 6. Preparation of Intermediate VIIb



## Step 1. Methyl-cyclohexane-d11-carboxylate (XIa)

A solution of commercially available cyclohexane-d11-carboxylic acid VIIa (1 g, 6.67 mmol, 1 equiv, CDN, 98 atom % D) in toluene (10 mL) was treated with SOCl<sub>2</sub> (0.5 mL, 6.8 mmol, 1.05 equiv). The mixture was heated at reflux for 2 hours and cooled to room temperature. Methanol (5 mL) was added, and the mixture was stirred for another 1 hour. The solvent was then evaporated yielding XIa (1 g, 91%) as a colorless oil.



## 29

Step 2. Methyl-2,2,3,3,4,4,5,5,6,6-d10-cyclohexanecarboxylate (XIb)

XIa (1 g, 6.1 mmol, 1 equiv) was dissolved in THF (10 mL) and cooled to  $-78^{\circ}\text{C}$ . LDA (12 mL, 1 M in THF, 12 mmol, 2 equiv) was added drop-wise. The mixture was stirred for 4 hours at  $-78^{\circ}\text{C}$ . then quenched with saturated  $\text{NH}_4\text{Cl}$  (10 mL) and warmed to room temperature. The mixture was extracted with ethyl acetate ( $3 \times 10$  mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and evaporated. The residue was resubjected to the above D/H exchange conditions. After the second exchange cycle, 1.1 g of crude XIb was obtained.

## Step 3.

2,2,3,3,4,4,5,5,6,6-d10-Cyclohexanecarboxylic acid (VIIb)

A solution of XIb (1 g, 6.1 mmol, 1 equiv, assumes 100% yield in previous step) in THF (10 mL) was treated with HCl (10 mL, 1M in water, 1.6 equiv). The reaction was heated at reflux overnight, then cooled to room temperature and concentrated to provide crude VIIb (0.8 g, 88.9%) which was used without purification.

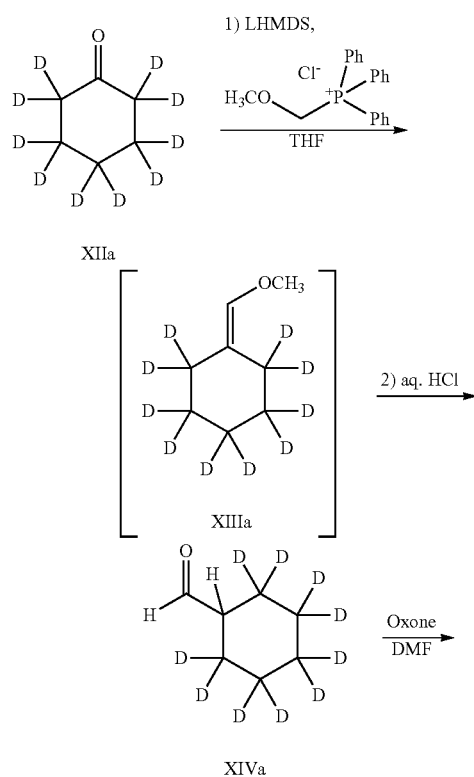
## Example 1a

## Synthesis of

2,2,3,3,4,4,5,5,6,6-d10-Cyclohexanecarboxylic acid (VIIb)

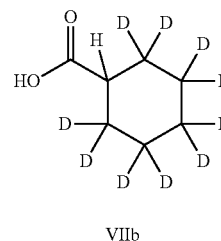
Intermediate VIIb was prepared as outlined in Scheme 6a below.

Scheme 6a. Preparation of Intermediate VIIb



## 30

-continued



## Step 1.

2,2,3,3,4,4,5,5,6,6-d10-cyclohexanecarbaldehyde (XIVa)

(Methoxymethyl)triphenylphosphonium chloride (13.48 g, 39.2 mmol, 1.1 equiv) was suspended in anhydrous THF (200 mL) and cooled to  $-78^{\circ}\text{C}$ . A solution of 1.0 M lithium bis(trimethylsilyl)amide in THF (39.2 mL, 39.2 mmol, 1.1 equiv) was added drop-wise over 0.5 hours. The reaction mixture was then stirred at  $-78^{\circ}\text{C}$  for another 2 hours followed by the addition of a solution of d10-cyclohexanone XIIa (3.8 g, 35.6 mmol, 1.0 equiv, CDN, 99 atom % D) in anhydrous THF (15 mL). The reaction was slowly warmed to room temperature and stirred overnight. GC-MS analysis confirmed conversion to XIIIa. Next, 2N HCl (60 mL) was added and the reaction was stirred for 1 hour, at which time GC-MS showed the complete conversion to XIVa. The reaction mixture was extracted with diethyl ether ( $100 \text{ mL} \times 4$ ). The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure at  $0-5^{\circ}\text{C}$  to give crude XIVa (14 g) as a yellow oil which was used directly in the next step.

## Step 2.

Cyclohexane-2,2,3,3,4,4,5,5,6,6-d10-carboxylic acid (VIIb)

A portion of crude XIVa (6 g, 9.3 mmol, assumes 100% yield in the previous step, 1 equiv) was dissolved in DMF (50 mL) followed by the addition of Oxone® reagent (17.8 g, 27.9 mmol, 3.0 equiv). The mixture was stirred at room temperature overnight followed by the addition of aqueous 1N HCl (100 mL). The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  ( $100 \text{ mL} \times 5$ ). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified via silica gel chromatography (0%-50% ethyl acetate in heptanes) to give VIIb, a colorless oil which solidified upon standing (0.49 g, 39% yield over 2 steps).

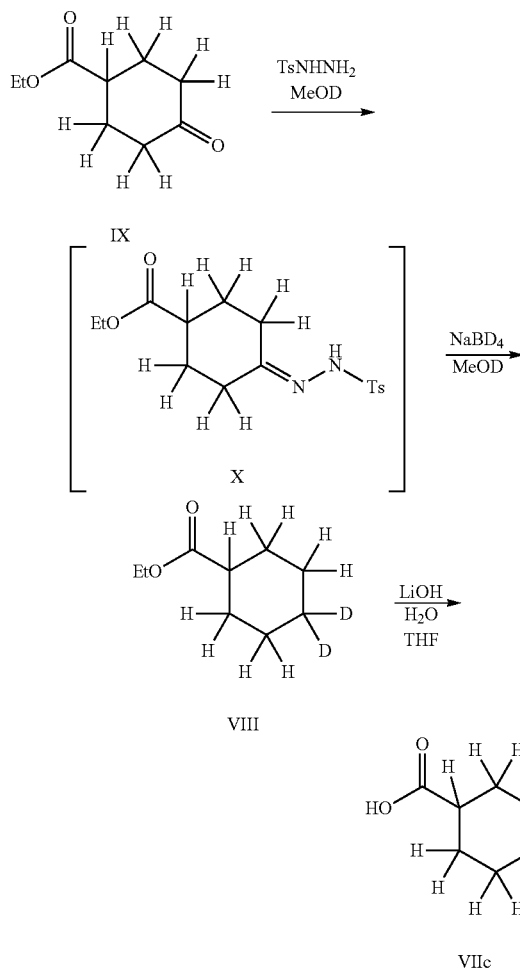
## Example 2

Synthesis of 4,4-d2-Cyclohexanecarboxylic acid (VIIc)

Intermediate VIIc was prepared as outlined in Scheme 7 below.

31

Scheme 7. Preparation of Intermediate VIIc



## Step 1. Ethyl-4,4-d2-cyclohexanecarboxylate (VIII)

Commercially available ethyl 4-oxocyclohexanecarboxylate IX (4.6 g, 27 mmol, 1.0 equiv) was dissolved in methanol-d<sub>1</sub> (50 mL, Cambridge Isotope Labs, 99 atom % D) followed by the addition of p-toluenesulfonyl hydrazide (5 g, 27 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h, and sodium borodeuteride (3.4 g, 81 mmol, 3.0 equiv, Cambridge Isotope Labs, 99 atom % D) was added to the reaction mixture. The mixture was stirred for 30 minutes at reflux, cooled to 0° C., quenched with an aqueous solution of 2N HCl (50 mL), and extracted with EtOAc (3×100 mL). The organic layer was washed with saturated aqueous NaHCO<sub>3</sub>, water, brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give VIII as a light yellow oil (3.6 g, 84% yield).

## Step 2. 4,4-d2-Cyclohexanecarboxylic acid (VIIc)

VIII (3.5 g, 22 mmol, 1.0 equiv) was dissolved in a solution of THF/water (1:1) (50 mL) followed by the addition of LiOH (2.1 g, 88 mmol, 4 equiv). The mixture was stirred for 3 hours at 65° C., cooled to room temperature, and acidified with aqueous 2N HCl to adjust the pH to 3. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×100 mL). The combined organic

32

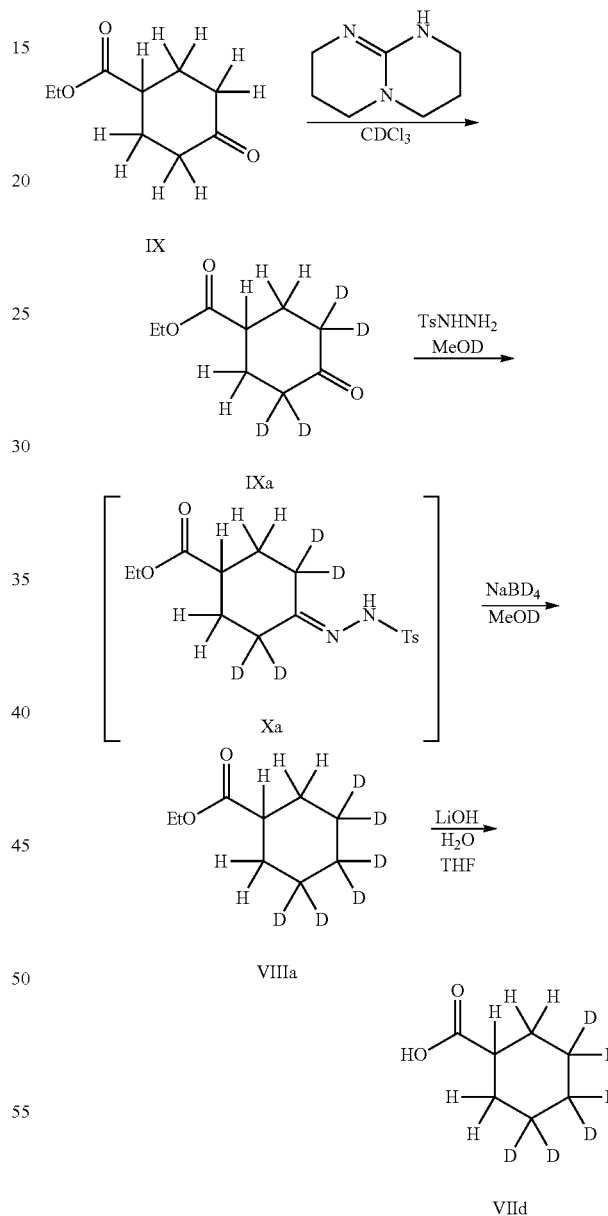
layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give VIIc as an off-white solid (1.6 g, 56% yield).

## Example 3

## Synthesis of 3,3,4,4,5,5-d6-Cyclohexanecarboxylic acid (VIIId)

Intermediate VIId was prepared as outlined in Scheme 8 below.

Scheme 8. Preparation of Intermediate VIId



## Step 1.

## Ethyl-3,3,5,5-d4-4-Oxocyclohexanecarboxylate (IXa)

Commercially available ethyl 4-oxocyclohexanecarboxylate IX (1.7 g, 10 mmol, 1.0 equiv) was dissolved in chloro-

## 33

form-d1 (25 mL, Cambridge Isotope Labs, 99.9 atom % D) followed by the addition of 2,3,4,6,7,8-hexahydro-1H-pyrimido[1,2-a]pyrimidine (140 mg, 1.0 mmol, 0.1 equiv). The reaction was stirred at room temperature for 1 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL), and washed with 1 N HCl (1×100 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting oil was purified by silica gel chromatography eluting with 10-40% ethyl acetate in heptanes. Proton NMR of the recovered product indicated that ~20% proton remained. A second exchange cycle was completed yielding IXa as a colorless liquid (1.3 g, 74% yield).

Step 2. Ethyl-3,3,4,4,5,5-d6-Cyclohexanecarboxylate (VIIIa)

Compound IXa (1.1 g, 6.3 mmol, 1.0 equiv) was dissolved in methanol-d1 (35 mL, Cambridge Isotope Labs, 99 atom % D) followed by the addition of p-toluenesulfonyl hydrazide (1.2 g, 6.3 mmol, 1.0 equiv). The mixture was stirred at room temperature for 1 h, and sodium borodeuteride (0.79 g, 18.9 mmol, 3.0 equiv, Cambridge Isotope Labs, 99 atom % D) was added to the reaction mixture. The mixture was stirred for 1 h at room temperature, cooled to 0° C., quenched with an aqueous solution of 1N HCl (10 mL), and extracted with EtOAc (3×100 mL). The combined organic layer was washed with saturated aqueous NaHCO<sub>3</sub>, water, brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to give Villa as an off-white semisolid (1.7 g, crude, 70% pure (<sup>1</sup>H NMR), used as such).

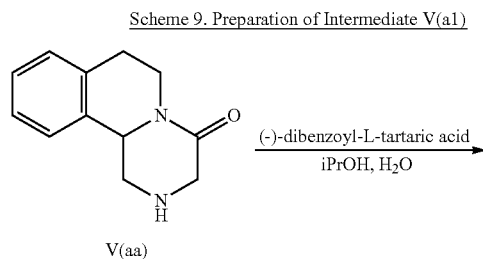
Step 3. 3,3,4,4,5,5-d6-Cyclohexanecarboxylic acid (VIIId)

Crude compound VIIIa (1.7 g, 6.3 mmol, 1.0 equiv, assumes 100% yield in previous step) was dissolved in a solution of THF/water (1:1) (30 mL) followed by the addition of LiOH (0.60 g, 25.2 mmol, 4 equiv). The mixture was stirred overnight at room temperature, diluted with water (50 mL), and extracted with MTBE (2×50 mL). The aqueous layer, was cooled to 0° C. and acidified with aqueous 1N HCl to adjust the pH to 3. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×50 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude material was purified via silica gel chromatography eluting with 10-50% ethyl acetate in heptanes to give VIIId as a colorless oil which solidified upon standing (0.55 g, 65% yield over 2 steps).

## Example 4

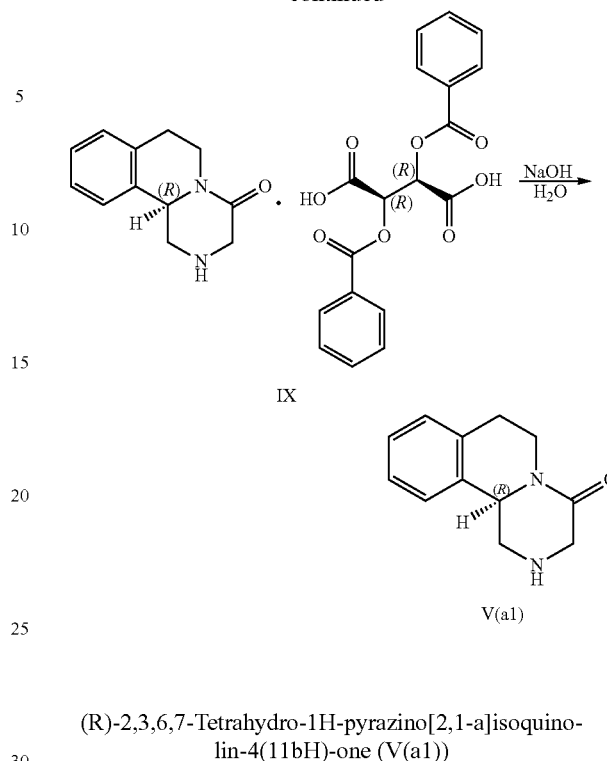
Synthesis of (R)-2,3,6,7-Tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (V(a1))

Intermediate V(a1) was prepared as outlined in Scheme 9 below.



## 34

-continued



This resolution was conducted in a manner similar to that described in the literature and on an open-source scientific website with the following URL: [http://www.ourexperiment.org/racres\\_pzq/1309/Multigramscale\\_racemic\\_resolution\\_of\\_praziquanamine\\_with\\_Dibenzoyl\\_tartaric\\_acid\\_MW4913.html](http://www.ourexperiment.org/racres_pzq/1309/Multigramscale_racemic_resolution_of_praziquanamine_with_Dibenzoyl_tartaric_acid_MW4913.html). Thus, V(aa) (4 g, 19.8 mmol, 1.0 equiv, prepared as described in Kim, J. H.; et al Tetrahedron 1998, 54(26), 7395-7400) was dissolved in a mixture of iPrOH (190 mL) and water (38 mL) followed by the addition of (-)-dibenzoyl-L-tartaric acid (7.1 g, 19.8 mmol, 1.0 equiv). The mixture was heated at 50-60° C. for 30 min. The mixture was then cooled in a water bath to room temperature and stirred for 4 hours. The solid was filtered and dried to give salt IX (3.8 g) as a white solid. Intermediate IX (3.8 g) was added to water (38 mL) and the stirred suspension was carefully adjusted to pH 10-11 by adding an aqueous solution of 2N NaOH. When the salt was completely dissolved the solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×25 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated to give V(a1) as a light yellow solid (1.9 g, yield 47.5%, 94% ee). The resolution procedure was repeated a second time to give V(a1) as a light yellow solid (1.7 g, recovery rate 89%, 99% ee).

## Example 5

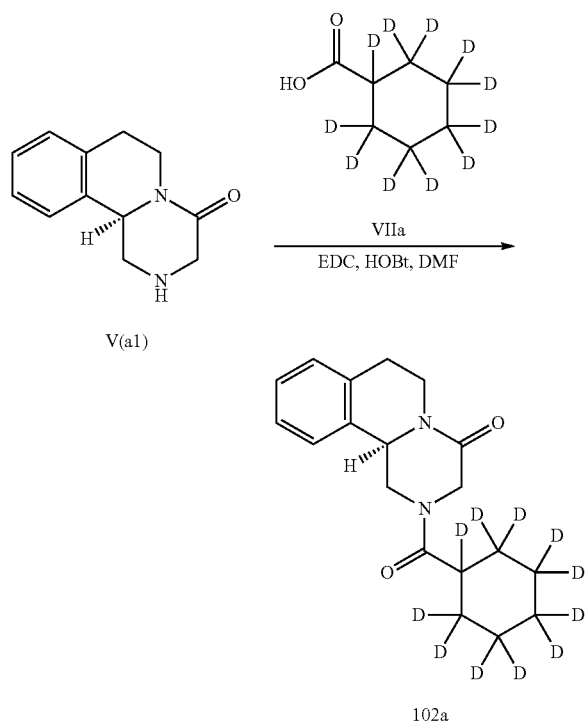
Synthesis of (R)-2-(Cyclohexane-d11-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (102a)

Compound 102a was prepared as outlined in Scheme 10 below.

35

36

Scheme 10. Preparation of Compound 102a



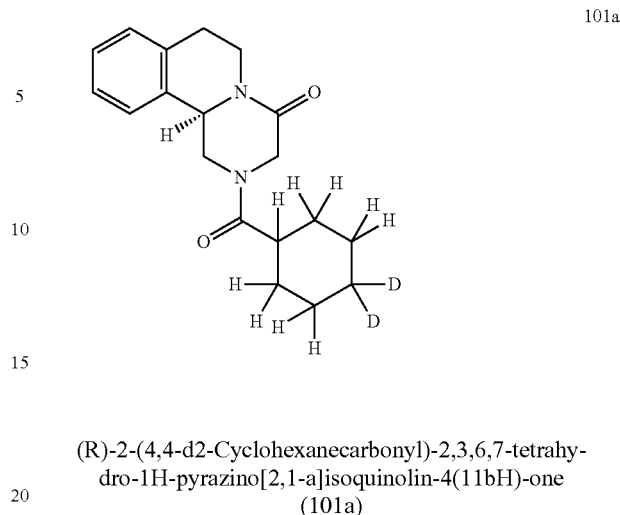
(R)-2-(Cyclohexane-d11-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (102a)

Commercially available cyclohexane-d11-carboxylic acid VIIa (240 mg, 1.73 mmol, 1.0 equiv, CDN, 98 atom % D) and V(a1) (350 mg, 1.73 mmol, 1.0 equiv) were dissolved in anhydrous DMF (20 mL) followed by the addition of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 400 mg, 2.1 mmol, 1.2 equiv) and hydroxybenzotriazole (HOBT, 280 mg, 2.1 mmol, 1.2 equiv). The mixture was stirred at room temperature overnight and diluted with ethyl acetate (100 mL). The mixture was washed with aqueous saturated  $\text{NH}_4\text{Cl}$ , aqueous saturated  $\text{NaHCO}_3$ , brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The resulting residue was purified via silica gel chromatography eluting with 0-30% ethyl acetate in heptanes to give 102a as a white solid (400 mg, 71% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.28-7.17 (m, 4H), 5.16 (d, 2H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), (minor rotational isomer also present); LCMS  $m/z$ =324  $[\text{M}+\text{H}]^+$ .

## Example 6

Synthesis of (R)-2-(4,4-d2-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (101a)

Compound 101a was prepared in a manner analogous to that outlined in Scheme 10 above.

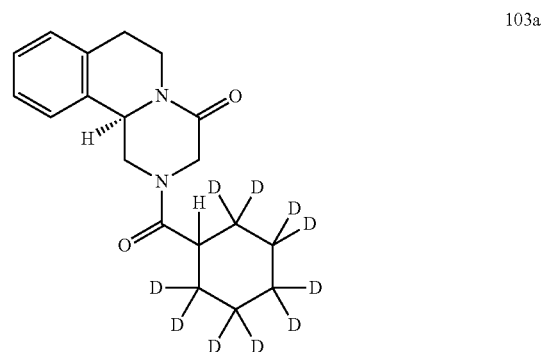


Compound 101a was prepared in an analogous fashion to Compound 102a from V(a1) and VIIc.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.28-7.17 (m, 4H), 5.16 (d, 2H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), 2.51 (t, 1H), 1.79 (t, 4H), 1.58 (t, 2H), 1.28 (t, 2H), (minor rotational isomer also present); LCMS  $m/z$ =315  $[\text{M}+\text{H}]^+$ .

## Example 7

Synthesis of (R)-2-(2,2,3,3,4,4,5,5,6,6-d10-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (103a)

Compound 103a was prepared in a manner analogous to that outlined in Scheme 10 above.



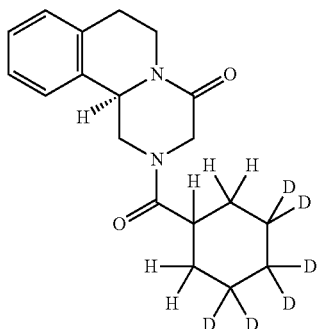
Compound 103a was prepared in a manner analogous to Compound 102a from V(a1) and VIIb.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 7.28-7.17 (m, 4H), 5.16 (d, 2H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), 2.44 (s, 1H), (minor rotational isomer also present); LCMS  $m/z$ =323  $[\text{M}+\text{H}]^+$ .

## 37

## Example 8

Synthesis of (R)-2-(3,3,4,4,5,5-d6-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (109a)

Compound 109a was prepared in a manner analogous to that outlined in Scheme 10 above.



(R)-2-(3,3,4,4,5,5-d6-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (109a)

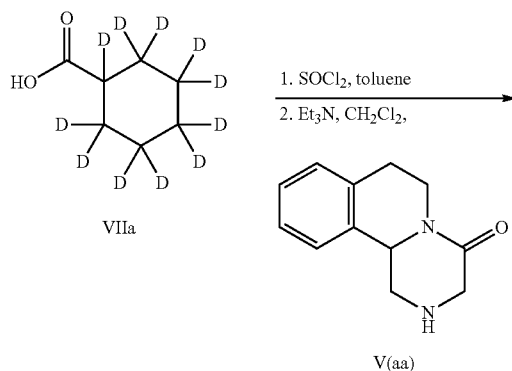
Compound 109a was prepared in an analogous fashion to Compound 102a from V(aa) and VIId. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm: 7.28-7.19 (m, 4H), 5.16 (d, 1H), 4.81 (m, 2H), 4.47 (d, 1H), 4.08 (d, 1H), 2.99-2.76 (M, 4H), 2.46 (t, 1H), 1.73 (m, 2H), 1.52 (m, 2H) (minor rotational isomer also present); LCMS m/z=319 [M+H]<sup>+</sup>.

## Example 9

Synthesis of 2-(Cyclohexane-d11-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (102)

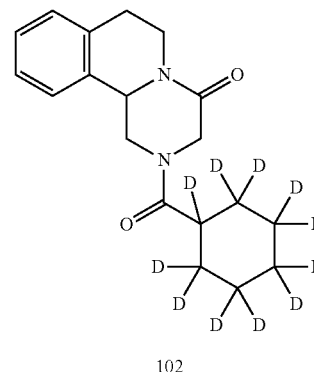
Compound 102 was prepared as outlined in Scheme 11 below.

Scheme 11. Preparation of Compound 102



## 38

## -continued



2-(Cyclohexane-d11-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (Compound 102)

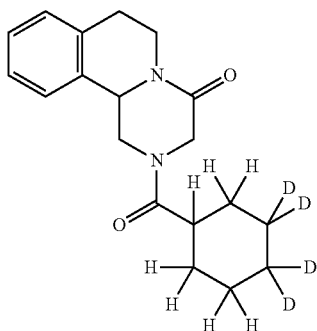
Commercially available cyclohexane-d11-carboxylic acid Vila (300 mg, 2.16 mmol, 1.0 equiv, CDN, 98 atom % D) was dissolved in anhydrous toluene (10 mL) followed by the addition of thionyl chloride (0.6 mL, 8.64 mmol, 4.0 equiv). The mixture was stirred at 60° C. for 1 hour and then concentrated under reduced pressure. The excess thionyl chloride was chased with toluene (2×10 mL). The resulting residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and cooled to 0° C. followed by the addition of a mixture of V(aa) (440 mg, 2.16 mmol, 1.0 equiv; prepared as described in Kim, J. H.; et al Tetrahedron 1998, 54(26), 7395-7400) and triethylamine (0.6 mL, 4.3 mmol, 2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The mixture was stirred at room temperature for 3 hours and quenched with aqueous saturated NaHCO<sub>3</sub> (20 mL). The organic layer was washed with brine, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The resulting residue was purified via silica gel chromatography eluting with 0-30% ethyl acetate in heptanes, and then recrystallized from ethyl acetate/heptanes (1:3) to give 102 as a white solid (300 mg, 44% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm: 7.28-7.17 (m, 4H), 5.16 (d, 1H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), (minor rotational isomer also present); LCMS m/z=324 [M+H]<sup>+</sup>.

## Example 10

Synthesis of 2-(4,4-d2-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (101)

Compound 101 was prepared in a manner analogous to that outlined in Scheme 10 above.

39



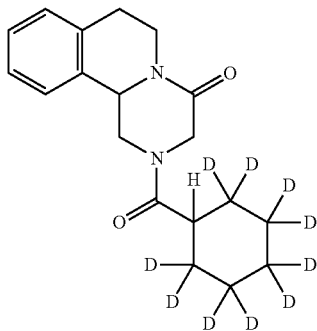
2-(Cyclohexane-4,4-d<sub>2</sub>-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (Compound 101)

Compound 101 was prepared in an analogous fashion to Compound 102a from V(aa) and VIIc. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm: 7.28-7.17 (m, 4H), 5.16 (d, 1H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), 2.51 (t, 1H), 1.79 (t, 4H), 1.58 (t, 2H), 1.28 (t, 2H), (minor rotational isomer also present); LCMS m/z=315 [M+H]<sup>+</sup>.

## Example 11

Synthesis of 2-(2,2,3,3,4,4,5,5,6,6-d<sub>10</sub>-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (103)

Compound 103 was prepared in a manner analogous to that outlined in Scheme 10 above.



2-(Cyclohexane-2,2,3,3,4,4,5,5,6,6-d<sub>10</sub>-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (Compound 103)

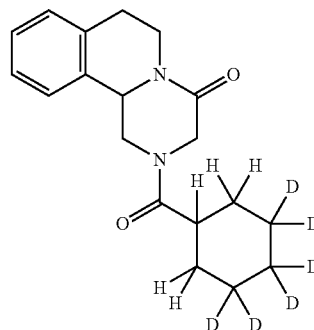
Compound 103 was prepared in an analogous fashion to Compound 102a from V(aa) and VIIb. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm: 7.28-7.17 (m, 4H), 5.16 (d, 1H), 4.80 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), 2.44 (s, 1H), (minor rotational isomer also present); LCMS m/z=323 [M+H]<sup>+</sup>.

40

## Example 12

Synthesis of 2-(3,3,4,4,5,5-d<sub>6</sub>-Cyclohexanecarbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (109)

Compound 109 was prepared in a manner analogous to that outlined in Scheme 10 above.



2-(Cyclohexane-3,3,4,4,5,5-d<sub>6</sub>-carbonyl)-2,3,6,7-tetrahydro-1H-pyrazino[2,1-a]isoquinolin-4(11bH)-one (Compound 109)

Compound 109 was prepared in an analogous fashion to Compound 102a from V(aa) and VIId. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ ppm: 7.28-7.19 (m, 4H), 5.16 (d, 1H), 4.81 (m, 2H), 4.47 (d, 1H), 4.07 (d, 1H), 3.00-2.79 (M, 4H), 2.46 (t, 1H), 1.72 (m, 2H), 1.52 (m, 2H) (minor rotational isomer also present); LCMS m/z=319 [M+H]<sup>+</sup>.

## Evaluation of Metabolic Stability

Certain in vitro liver metabolism studies have been described previously in the following references, each of which is incorporated herein in their entirety: Obach, R S, Drug Metab Disp, 1999, 27:1350; Houston, J B et al., Drug Metab Rev, 1997, 29:891; Houston, J B, Biochem Pharmacol, 1994, 47:1469; Iwatsubo, T et al., Pharmacol Ther, 1997, 73:147; and Lave, T, et al., Pharm Res, 1997, 14:152.

## Microsomal Assay:

Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, Kans.). β-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl<sub>2</sub>), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

## Determination of Metabolic Stability:

7.5 mM stock solutions of test compounds were prepared in DMSO. The 7.5 mM stock solutions were diluted to 50 μM in acetonitrile (ACN). The 20 mg/mL human liver microsomes were diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl<sub>2</sub>. The diluted microsomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μL aliquot of the 50 μM test compound was added to the microsomes and the mixture was pre-warmed for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 0.5 mg/mL human liver microsomes, 1.0 μM test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM MgCl<sub>2</sub>. The reaction mixtures were incubated at 37° C., and 50 μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which con-

## 41

tained 50  $\mu$ L of ice-cold ACN with internal standard to stop the reactions. The plates were stored at 4° C. for 20 minutes after which 100  $\mu$ L of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure was followed for praziquantel and the positive control, 7-ethoxycoumarin (1  $\mu$ M). Testing was done in triplicate.

## Data Analysis:

The in vitro half-lives ( $t_{1/2}$ s) for test compounds were calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship:

$$\text{in vitro } t_{1/2} = 0.693/k, \text{ where } k = -[\text{slope of linear regression of \% parent remaining (ln) vs incubation time}]$$

The results of the HLM assays are shown in Tables 1-3. Table 1 shows the results of the  $t_{1/2}$  values measured in HLM for praziquantel and for Compounds 101 and 102. Table 2 shows the results of the VA values measured in HLM for praziquantel for Compounds 101, 109, 103 and 102. Table 3 shows the results of the  $t_{1/2}$  values measured in HLM for praziquantel and (R)-praziquantel and for Compounds 101(a), 109(a), 103(a) and 102(a). For each table, the VA values in each of four runs, as well as the average values, are provided together with the percentage increase in the VA value relative to a non-deuterated compound (praziquantel and/or (R)-praziquantel.

TABLE 1

Half-life ( $t_{1/2}$ ) values measured in Human Liver Microsomes					
Compound	$t_{1/2}$ (min)				AVE $\pm$ SD and % increase in AVE relative to praziquantel
	Run No. 1	Run No. 2	Run No. 3	Run No. 4	
Praziquantel	36.2	37.3	37.3	44.7	38.9 $\pm$ 3.9
101	47.4	43.6	43.1	52.7	46.7 $\pm$ 4.4 20%
102	56.4	55.4	44.8	66.2	55.7 $\pm$ 8.7 43%

TABLE 2

Half-life ( $t_{1/2}$ ) values measured in Human Liver Microsomes					
Compound	$t_{1/2}$ (min)				AVE $\pm$ SD and % increase in AVE relative to praziquantel
	Run No. 5	Run No. 6	Run No. 7	Run No. 8	
Praziquantel	41.2	43.8	30.6	36.9	38.1 $\pm$ 5.8
101	56.7	53.9	38.2	60.1	52.2 $\pm$ 9.7 37%
109	55.7	53.5	46.4	51.2	52.2 $\pm$ 4.6 37%
103	65.1	51.6	60.6	69.3	61.7 $\pm$ 7.6 62%
102	54.8	50.6	44.9	52.4	50.7 $\pm$ 4.2 33%

## 42

TABLE 3

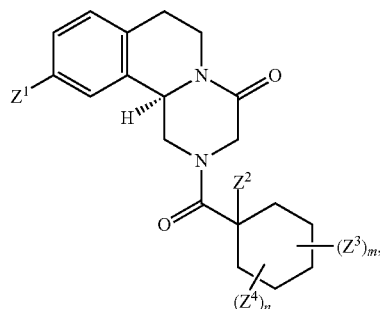
Half-life ( $t_{1/2}$ ) values measured in Human Liver Microsomes					
Compound ID	Run No. 9	Run No. 10	Run No. 11	Run No. 12	AVE $\pm$ SD and % increase in AVE a) relative to praziquantel, and b) relative to (R)-praziquantel
Praziquantel (R)	29.5	31.5	35.1	30.5	31.7 $\pm$ 2.5
Praziquantel 101(a)	37.5	36.4	40.0	41.8	38.2 $\pm$ 2.5
	48.9	46.7	56.3	45.8	49.4 $\pm$ 4.8 a) 56% b) 29%
109(a)	39.5	38.7	43.2	55.4	44.2 $\pm$ 7.7 a) 40% b) 16%
103(a)	52.7	41.8	50.0	55.5	50.0 $\pm$ 5.9 a) 58% b) 31%
102(a)	57.4	53.6	50.1	46.0	51.8 $\pm$ 4.9 a) 64% b) 36%

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of Formula I or Ia and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

What is claimed is:

1. A method of disrupting cell permeability to calcium ions in a parasitic cell, comprising contacting said cell with a compound of Formula Ia:

Formula Ia



or a pharmaceutically acceptable salt thereof, wherein:

$Z^1$  is hydrogen or fluorine;

$Z^2$  is hydrogen, deuterium, or fluorine;

$Z^3$  is deuterium;

$Z^4$  is fluorine;

m is 2, 4, 6, 8 or 10; and

n is 0 or 2;

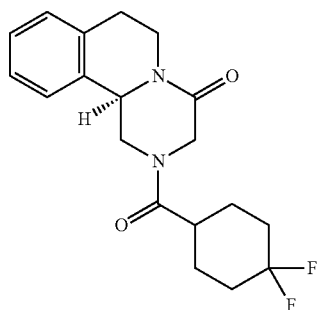
provided that:

the sum of m and n does not exceed 10.

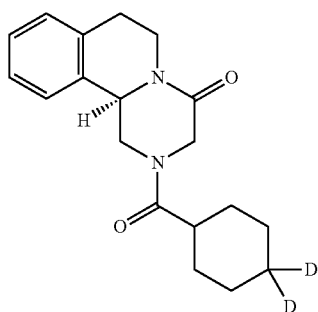
2. The method of claim 1, wherein 2, 4, 6, 8 or 10 geminal  $Z^3$  are present.

**43**

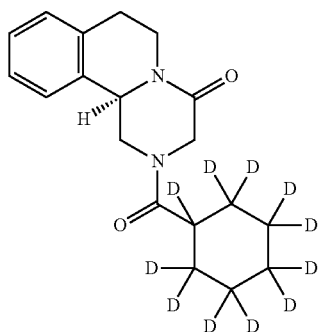
3. The method of claim 1, wherein  $Z^2$  is hydrogen.  
 4. The method of claim 1, wherein  $Z^2$  is deuterium.  
 5. The method of claim 1, wherein 2 geminal  $Z^4$  are present.  
 6. The method of claim 1, wherein the compound is selected from any one of the following compounds:



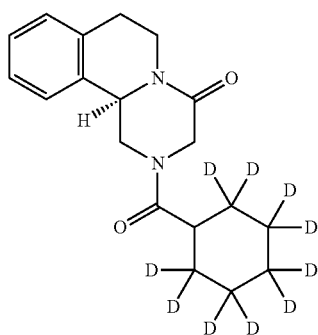
100(a) 10



101(a) 25



102(a) 40

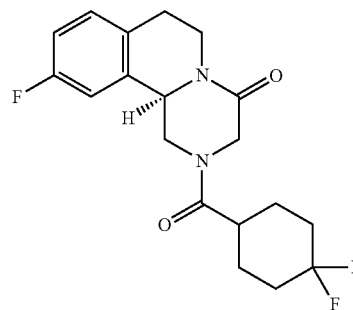


103(a) 55

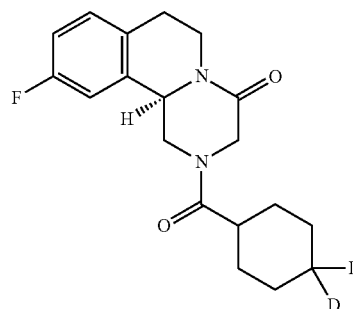
**44**

-continued

104(a)

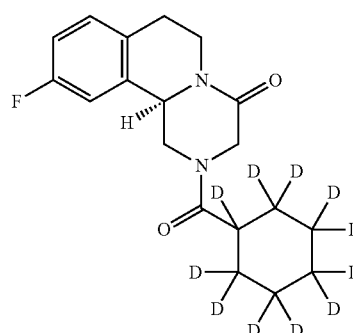


15



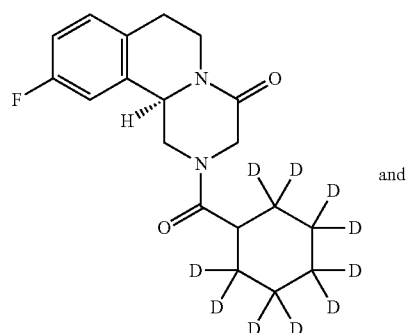
105(a)

20



106(a)

35



107(a)

45

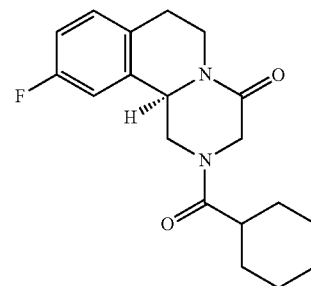
50

103(a)

55

60

65



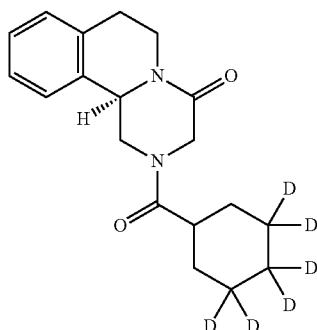
108(a)

or a pharmaceutically acceptable salt thereof.

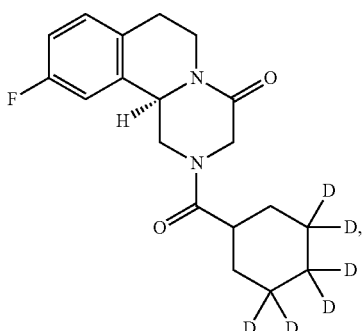


45

7. The method of claim 1, wherein the compound is selected from the following compounds:



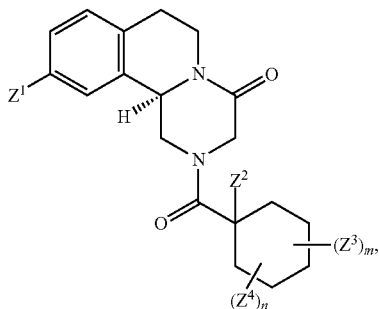
and



or a pharmaceutically acceptable salt thereof.

8. A method of treating a disease or condition selected from *schistosoma* infections, infections due to *Clonorchis sinensis* or *Opisthorchis viverrini*; cysticercosis; neurocysticercosis; and malaria, in a patient in need thereof comprising the step of administering to said patient an effective amount of a compound of Formula Ia:

Formula Ia



or a pharmaceutically acceptable salt thereof, wherein:

- Z<sup>1</sup> is hydrogen or fluorine;
- Z<sup>2</sup> is hydrogen, deuterium, or fluorine;
- Z<sup>3</sup> is deuterium;
- Z<sup>4</sup> is fluorine;
- m is 2, 4, 6, 8 or 10; and
- n is 0 or 2;

provided that:

the sum of m and n does not exceed 10.

9. The method of claim 8, wherein 2, 4, 6, 8 or 10 geminal Z<sup>3</sup> are present.

46

10. The method of claim 8, wherein Z<sup>2</sup> is hydrogen.

11. The method of claim 8, wherein Z<sup>2</sup> is deuterium.

12. The method of claim 8, wherein 2 geminal Z<sup>4</sup> are present.

13. The method of claim 8, wherein the compound is selected from any one of the following compounds:

109(a)

10

15

110(a)

20

25

30

100(a)

101(a)

102(a)

40

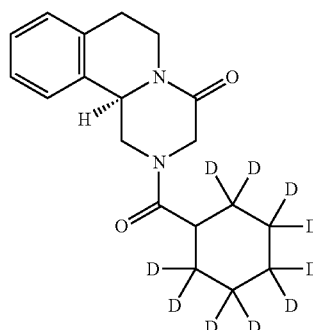
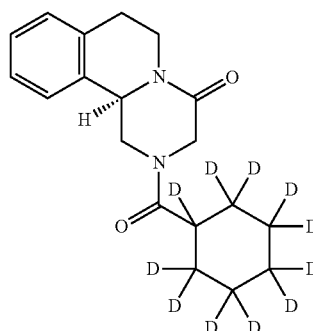
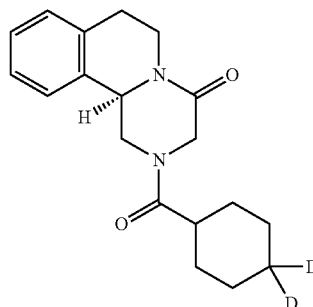
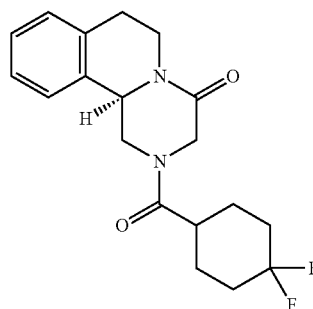
45

50

55

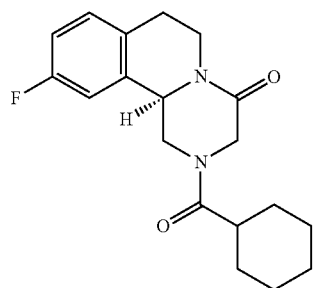
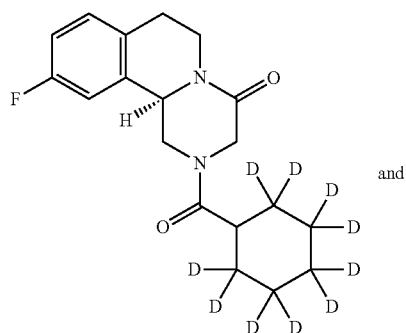
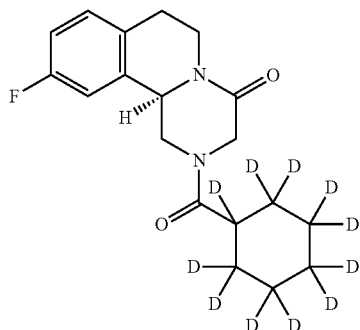
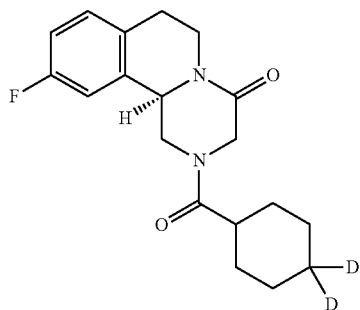
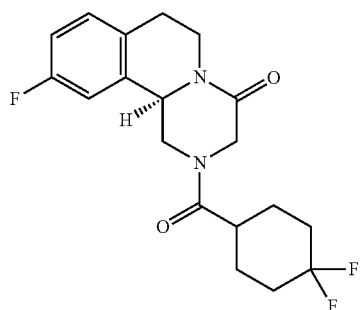
60

65



47

-continued



or a pharmaceutically acceptable salt thereof.

48

14. The method of claim 8, wherein the compound is selected from the following compounds:

104(a)

5

109(a)

10

and

105(a)

15

20

25

106(a)

30

107(a)

40

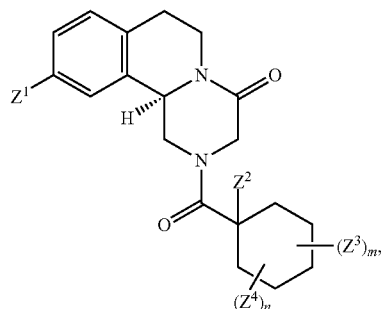
45

Formula Ia

50

108(a)

55



60 or a pharmaceutically acceptable salt thereof, wherein:

Z<sup>1</sup> is hydrogen or fluorine;

Z<sup>2</sup> is hydrogen, deuterium, or fluorine;

Z<sup>3</sup> is deuterium;

Z<sup>4</sup> is fluorine;

m is 2, 4, 6, 8 or 10; and

n is 0 or 2;

49

provided that:

the sum of m and n does not exceed 10.

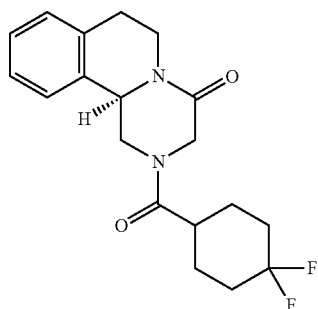
16. The method of claim 15, wherein 2, 4, 6, 8 or 10 geminal Z<sup>3</sup> are present.

17. The method of claim 15, wherein Z<sup>2</sup> is hydrogen.

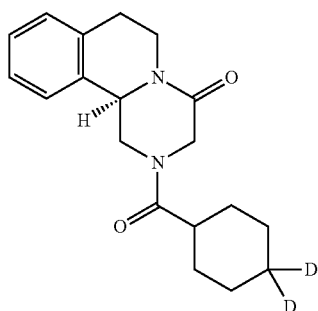
18. The method of claim 15, wherein Z<sup>2</sup> is deuterium.

19. The method of claim 15, wherein 2 geminal Z<sup>4</sup> are present.

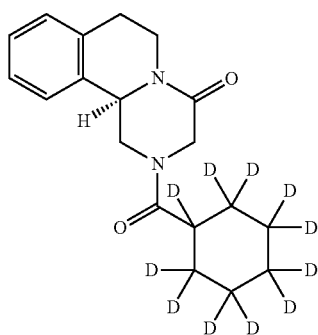
20. The method of claim 15, wherein the compound is selected from any one of the following compounds:



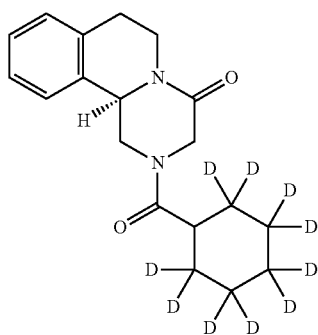
100(a) 15



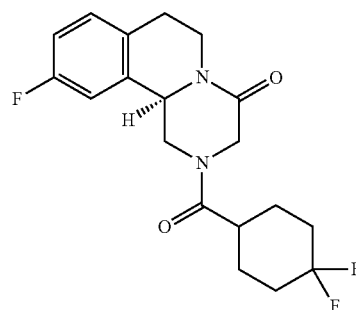
101(a) 20



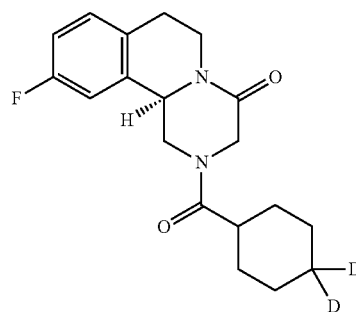
102(a) 25



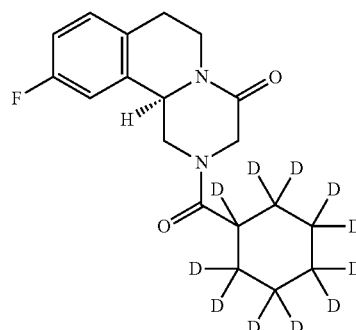
103(a) 30



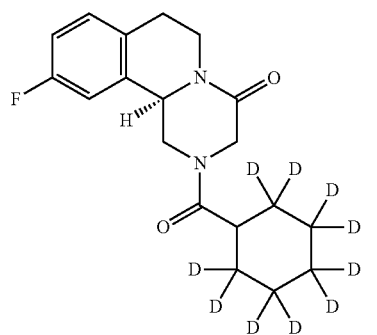
104(a)



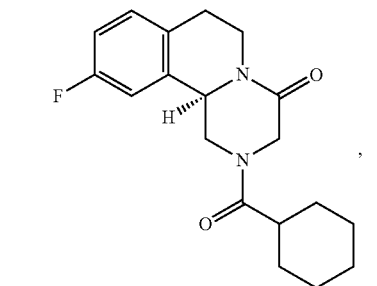
105(a)



106(a)



107(a)

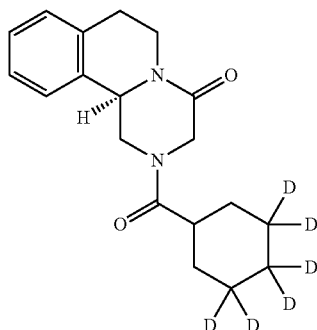


108(a)

or a pharmaceutically acceptable salt thereof.

**51**

**21.** The method of claim **15**, wherein the compound is selected from the following compounds:



and

**52**

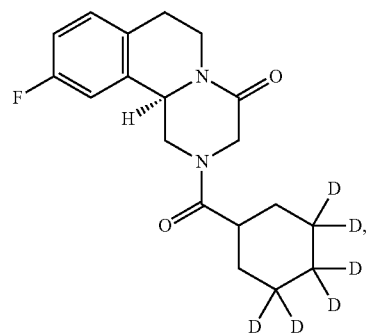
-continued

110(a)

109(a) 5

10

15



or a pharmaceutically acceptable salt thereof.

\* \* \* \* \*